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I. GENETICS

CLINIC AND GENETIC HETEROGENEITY IN EHLERS-DANLOS SYNDROME

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Abstract

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of hereditable connective tissue disorders characterized by articular hypermobility, skin hyperextensibility, and tissue fragility. EDS type IV being the most life-threatening form. It is characterized by a type III collagen deficiency and this disease involves a col3A1 gene mutation (5, 6). We report the case of a 47 year-old woman with type IV EDS. Each of her two children presented clinical elements of EDS: her daughter (25 years old) and her son (18 years old). Clinic and genetic heterogeneity of the disease is very evident in this family, the three family members presenting clinical symptoms and comorbidities which made difficult the attempt to integrate them in a certain EDS type; these three cases presented a various clinical expression and severity. Another particularity is also represented by the presence and high frequency of associated spontaneous bone fractures.

Key word: Ehlers-Danlos syndrome, genetic heterogeneity, gene COL3A1.

Background

Ehlers-Danlos syndrome (EDS) refers to a group of disorders linked by genetic defects that affect collagen structure and function. Collagen is a major protein in the body and forms the base foundation for connective tissues. Owing to a genetic defect in collagen manufacture, tissues affected are abnormally weak, depending on the specific genetic defect. Major symptoms can include skin fragility, excessive skin stretchability, and excessively loose joints. Some types of EDS are characterized by fragile blood vessels or abnormal spine curvature (3).

Collagen is a strong, fibrous protein that lends strength and elasticity to connective tissues such as the skin, tendons, organ walls, cartilage, and blood vessels. Each of these connective tissues requires collagen tailored to meet its specific purposes. The many roles of collagen are reflected in the number of genes dedicated to its production. There are at least 28 genes in humans that encode 16 different types of collagen. Defects in these genes can affect basic construction as well as the fine-tuned processing of the collagen (7).

According to the Ehlers-Danlos National Foundation, 1 in 5,000 to 1 in 10,000 people are affected by some form of EDS. EDS is an inherited disease, and its pattern depends on the affected gene (1). There are three types of inherited patterns: autosomal dominant, autosomal recessive, and X-linked (extremely rare).

Up until 1997, the types of Ehlers-Danlos Syndrome were classed from numbers I-XI. However, after the New Nosology was released in 1997, the types were described under different names, eg. Classical type EDS (formerly types I and II), or Hypermobility type EDS (formerly type III). It is generally thought that one can only have on type of EDS, but more and more people are manifesting more than one type at the same time, challenging this logic.

The new classification is simpler and based more on descriptions of the actual symptoms. EDS is now classified into six major types: classical, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis, and a collection of rare or poorly defined varieties (4).

Formerly called EDS type IV, EDS vascular type carries the risk of premature death. The connective tissue in the intestines, arteries, and uterus is unusually weak, leading to a strong possibility of organ or blood vessel rupture. Such ruptures are more likely between ages 20–40, although they can occur any time, and can be life-threatening. The large joints have normal stability, but small joints in the hands and feet are loose. The skin is thin and translucent, with veins dramatically visible. The skin bruises easily. Other complications can include collapsed lungs, premature aging of the skin on the hands and feet, formation of openings between arteries and veins, and complications following surgery. EDS vascular type is inherited in an autosomal dominant manner (2).

Case report

We report the case of a 47 year-old woman with type IV EDS.

Familial history: The parents are not consanguineous first cousins. Her father had a clinical features of EDS, also, the grandfather and two brothers showed varying degrees of joint and skin hyperextensibility (fig. 1).

The medical history of our patient included multiple spontaneous bone fractures, anomalies of

subclavian artery (fig. 3, 4), moderate bruising and rupture of hollow organs such as the intestine and stomach, requiring repeated surgical interventions, generalized joint hypermobility (fig. 2), skin hyperextensibility, chronic joint pain, recurrent joint dislocations, extensive bruising, characteristic facial appearance, varicose veins, progressive scoliosis, osteopenia. Each of her two children presented clinical elements of EDS: her daughter (25 years old) presented especially molluscoid pseudotumours, these are firm, fibrous lumps measuring up to 2 - 3 cm which develop over pressure points such as the elbows and knees, subcutaneous spheroids. Approximately one third of affected individuals describe small, firm nodules like 'ball-bearings' just beneath the skin. These consist of fibrotic and calcified fat which overlay bony areas such as the shins, (skin biopsy, fig. 5-6-7), joint hypermobility, chronic joint pain with recurrent joint dislocations, easy bruising and spontaneous bone fractures. Her son (18 years old) presented recurrent joint dislocations, moderate skin hyperextensibilty, articular hypermobility and autism.

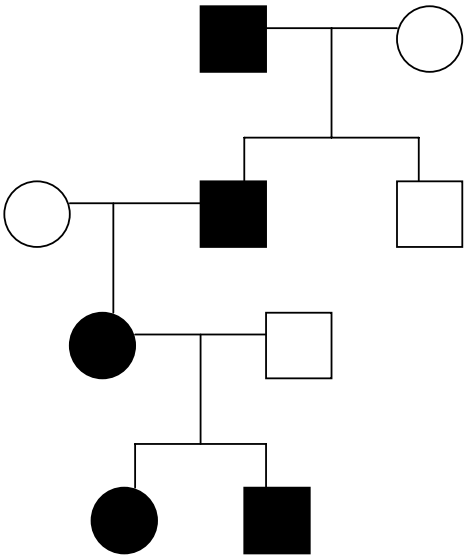

Fig. 1. Pedigree chart of a 47 year-old woman with type IV EDS.

Fig. 2. Generalized joint hypermobility.

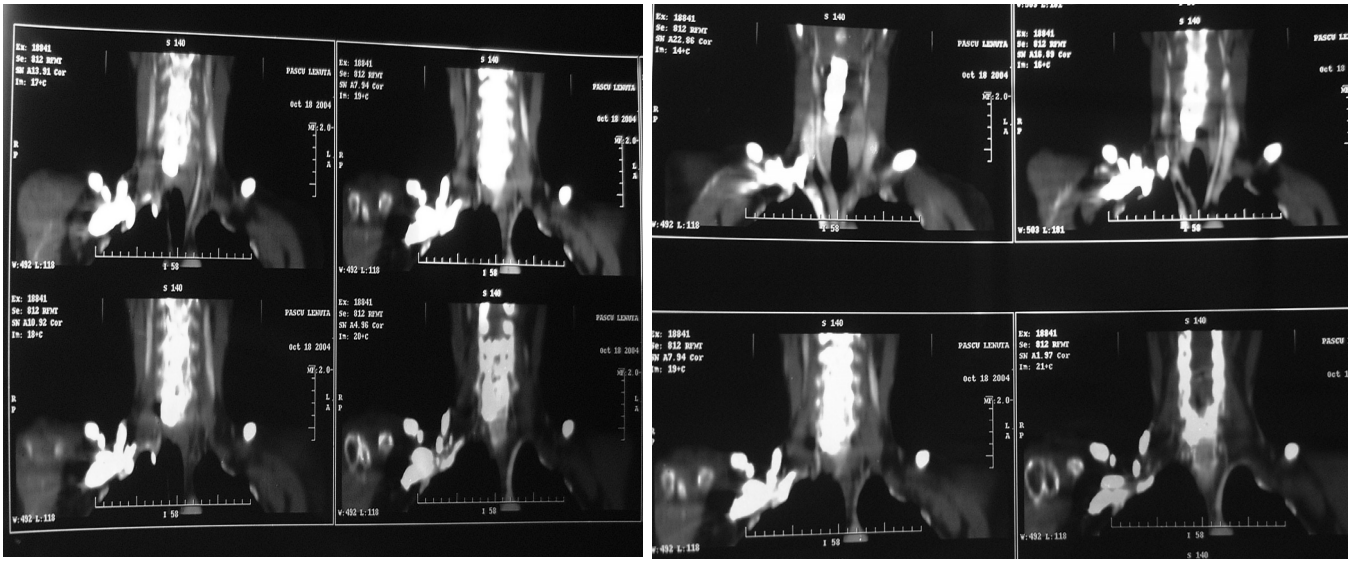

Fig. 3-4. MRI: Anomalies of subclavian artery

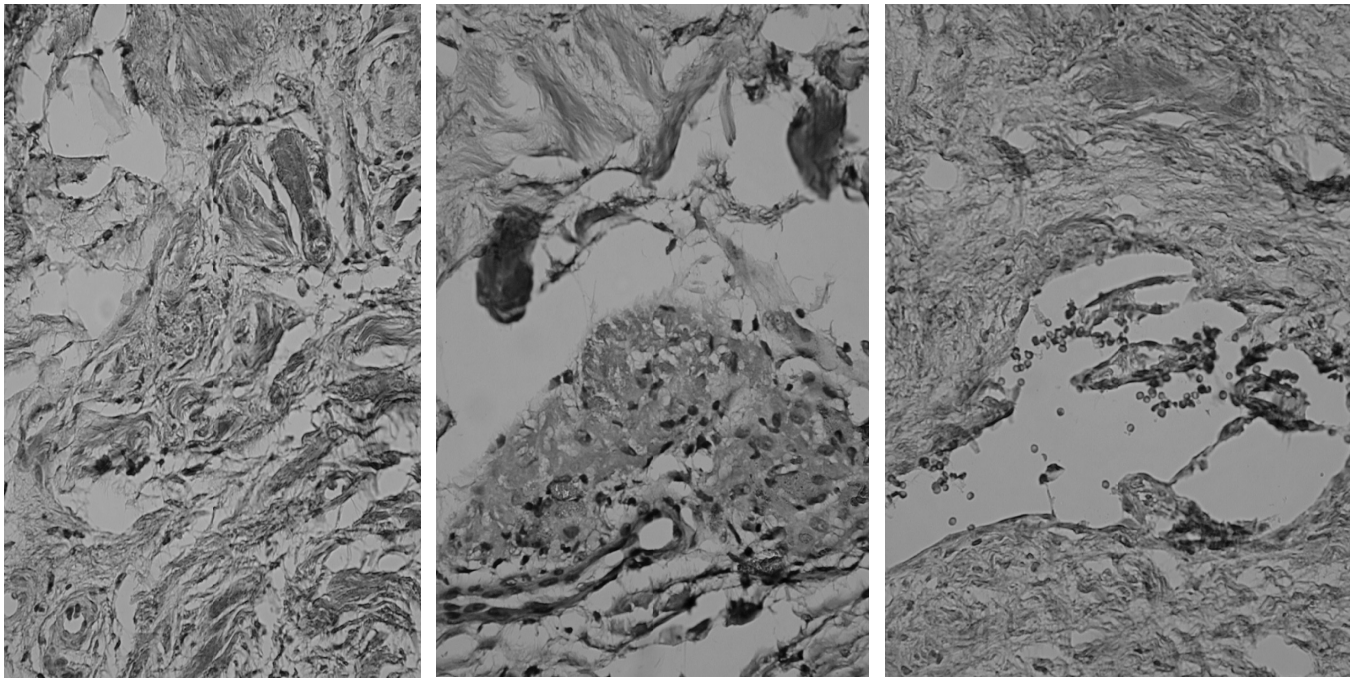

Fig. 5-6-7. Skin biopsy of molluscoid pseudotumours (daughter, 25 years old) revealing proportional increase in elastic fibers consistent with EDS.

Discussions:

Diagnosis of EDS in this family is based upon clinical findings, upon the family history, skin biopsy of molluscoid pseudotumours and other paraclinic investigations (MRI).

This three patients do not fit neatly into one of the specific types of EDS, a diagnosis is often delayed or overlooked. Specific diagnostic tests are available for some types of EDS in which there is a known biochemical defect, like in this case, but we don't have the possibility to test this. In the same time, the skin biopsy helps us to study the chemical makeup of the connective tissue. The biopsy involves removing a small piece of skin, under local anesthesia. To diagnose EDS it is necessary to have a good team of medical geneticists, pediatricians, rheumatologists, pathologists, cardiologists and dermatologists.

Since EDS is a genetic disorder it cannot be prevented. However, some of the complications of the disorder can be avoided to a certain degree. Prior to having children, individuals with EDS should consult their physicians and a genetic counselor to investigate the risks to themselves and to their potential children.

Clinic and genetic heterogeneity of the disease is very evident in this family, the three family members presenting clinical symptoms and comorbidities which made difficult the attempt to integrate them in a certain EDS type; these three cases presented a various clinical expression and severity. Another particularity is also represented by the presence and high frequency of associated spontaneous bone fractures. Molecular investigations could probably explain the mechanism which associates Osteogenesis Imperfecta signs to EDS symptomps, but we couldn't perform these investigations for the time (9).

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II. NEONATOLOGY

POSITIVE DIAGNOSIS OF DANDY - WALKER SYNDROME

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Abstracts

Dandy - Walker syndrome is a rare affection in newborn pathology and due to its neuropathologic implications and central nervous system associated anomalies early diagnosis is very important. The most important complication is evolving hydrocephalus, characterized by occipital prominence of the skull.

The authors would like, in the present work, to highlight the importance of prenatal and neonatal ultrasonography in early diagnosis of Dandy Walker syndrome and of central nervous system associated anomalies.

Key words: Dandy-Walker Syndrome, ultrasound scan.

Introduction

The Dandy- Walker complex includes the Dandy-Walker malformation and the variant of Dandy - Walker syndrome. Dandy- Walker malformation consists of enlargement of the posterior fossa as a result of the cystic dilatation of the fourth ventricle in partial or total agenesis of the cerebellar vermis. In approximate 5 - 10 % of the cases congenital hydrocephalus is determined. The Dandy - Walker variant is characterized by light enlargement of a posterior fossa, a cyst of the posterior fossa continuing the fourth ventricle which is united with through a narrow duct and a disgenetic cerebellar vermis.

In Dandy- Walker malformation several associated anomalies occur (70 % of cases); most frequent are: agenesis of the corpus callosum and the variant of neuronal migration disorders.

Neuropathology

Fundamental anomaly of the posterior brain is related with the wrong forming of the cerebellar vermis and the roof of the fourth ventricle. The start point of the malformation seems to be, mainly, a delay or a failure in opening Magendie's orifice which leads CSF storage and cystic dilatation of the fourth ventricle. Despite the subsequent opening of the foramina of Luschka (usually opened in Dandy- Walker malformation) the cystic dilatation of the fourth ventricle and CSF leaking persists (fig.1 and fig.2).

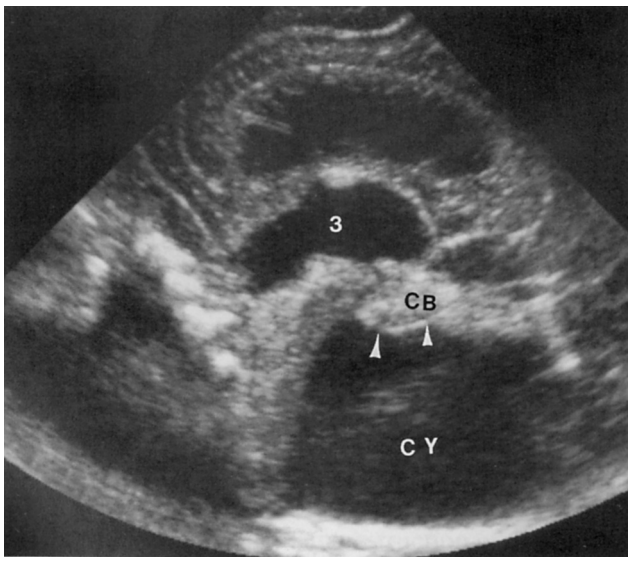

Fig. 1. Dandy- Walker malformation. A cyst of posterior fossa.

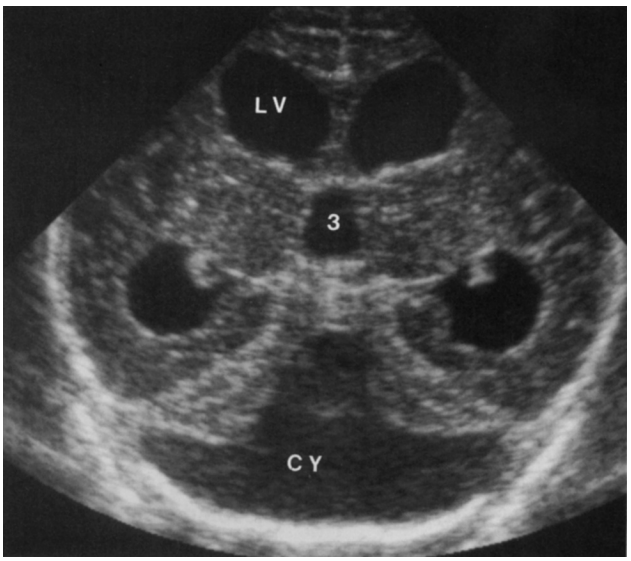

Fig. 2. Coronal posterior scan. A large cystic structure; behind - the compressed cerebellar vermis.

Appearance of the Dandy- Walker malformation is not cleared yet; nevertheless, the period of maximum development of the orifices is the second and the third month of gestation, during the prosencephalic development. This period coincides with neuronal migration explaining in this way the association of Dandy- Walker malformation with agenesis of the corpus callosum and neuronal migration disorders.

Dandy- Walker syndrome – neuropathology

Primary injuries	Cystic dilatation of the fourth ventricle Agenesis of the vermis Hydrocephalus
Associated injuries	Agenesis of the corpus callosum (20-30%) Cerebral neuronal heterotopia (aprox. 15%) Aqueductal stenosis (aprox.5-10%) Cerebral gyral anomaly (aprox.10%) Syringomyelia (aprox. 5-10%) Occipital encephalocele (aprox.10-15%) Inferior olivary anomalies or dentate nuclei (aprox.20%) One or more associated (70%)

Positive diagnosis

Clinical dominant feature is hydrocephalus, characterized by occipital prominence of the skull and large dilatation of the fourth ventricle with enlargement of the posterior fossa. Marked hydrocephalus is present at few cases in neonatal period. Use on a large scale of prenatal and neonatal ultrasonography allowed the track down of several cases since intrauterine and early neonatal period, despite the absence of the quickly head growing and intracranial hypertension signs, which usually appear after first year of life. In some situations hydrocephalus can appear only in maturity period. Association of other anomalies of central nervous system and systemic malformations represents another clinical aspect. Amongst these cardiac disorders and renals are the most frequent, 20-30% from the cases with postnatal diagnosis and 60-80% from the cases with prenatal ultrasonography. Dandy - Walker variant results from a limited disorder of cerebellar hemispheres. Patients with both anomalies can present a development delay and an increasing of head circumference. The neurological development delay depends on the severity of the associated supratentorial anomalies: hydrocephalus, agenesis of the corpus callosum, gray matter heterotopia, polymicrogyria and occipital encephalocele. Hydrocephalus could be present at birth but more frequently it develops later, 75% of patients appearing after three month from birth. Regarding systemic anomalies the most frequent are cardiac anomalies and polydactyly.

Echographic manifestations of the disorder are better seen in sagital sections, especially medium sagital and they are represented by:

- a cyst of posterior fossa, big, with liquid, homogeneous, which is in the baloon-shape fourth ventricle;
- partial or complete absence of vermis;
- cerebellar hemispheres hypoplasia ;
- tentorium raising.

In the coronar section is confirmed the presence of a posterior fossa cyst and high position of the tentorium (fig. 3).

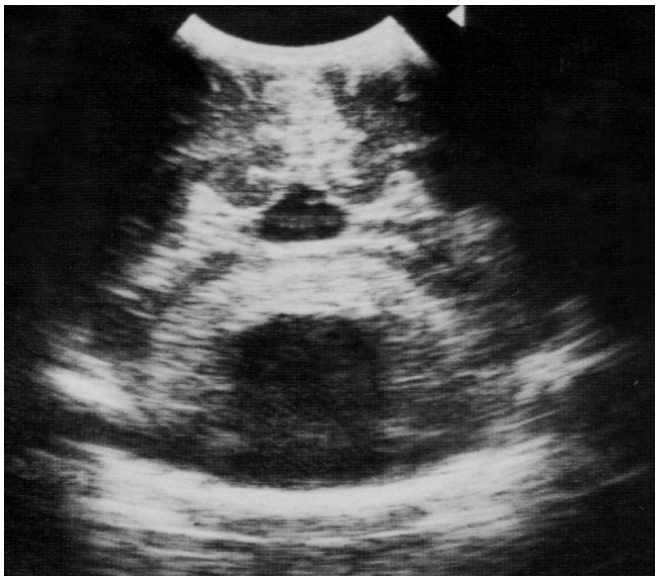

Fig. 3. Coronal posterior scan. Premature baby with congenital hydrocephalus. A large cystic structure is present.

Differential diagnosis:

Arachnoid cyst of posterior fossa and dilatation of the large cisterna, situation when cerebellar vermis and the fourth ventricle are not affected. In the Dandy-Walker variant the two cerebellar hemispheres, hypoplasic, in sagital section, could give the impression of a normal vermis. The frontal sections and the CT through posterior fossa will mark a narrow duct between anterior aria of the fourth ventricle and the rest of the posterior fossa, absence of vermis respectively.

Conclusions

1. Dandy Walker syndrome is a rare disease in medical practice, but fortunately can be easily detected by ultrasound exam.
2. Associated malformations are common especially neurological malformations: agenesis of corpus calos, disorders in the process of neural migration, occipital encephalocel.
3. Evolutive hidrocephaly is the most severe complication, it can occur at birth, but in 75 % the anomaly appears after the age of 3 months.

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PERINATAL ASPECTS IN NEWBORN RESULTING FROM ASSISTED HUMAN REPRODUCTION

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Abstract

The paper present the main aspects of perinatale evolution of new – born resulting from assisted human reproduction compared with those resulting from natural reproduction in Vitro Fertilization Center within the Obstetrics – Gynecology Clinic „Bega" Timişoara. The study validates The results obtains during 10 years of experience in the team of the country first in Vitro Fertilization Center.

The researched material is represented by a group of 109 new – born resulting from assisted human reproduction who were delivered in the clinic. These cases were completely monitored until going home. A control group (n = 95) represented by new – born resulted from natural reproduction was used for the factorial analysis and the accuracy of the results. The method of controlled comparative research was used (case - with ness). The main perinatal risk factors as well as the evolution parameters of the new – born during the first week of life have been analyzes.

There are no significant differences for most of the analyzed parameters between the cases of the two groups. Important differences were registered for: the average age of the mother (higher in the researched group); the monitorization of the gestation evolution (better in the research group); delivery through caesarian section (more frequent in the research group); the incidence of prematurity and intrauterine growth limitation and their perinatal/neonatal consequence (higher and more important in the research group); the incidence of multiples pregnancies (exclusively in the research group). The results are validated by the size of the groups and the analyzed method.

The results of the study show that the perinatal evolution of the new – born is mostly independent of the way of conception and it depends on the feto – neonatal status of the perinatal period. Assisted human reproduction represents a great victory of medicine against sterility.

Key words: newborns, human assisted reproduction.

Introduction. Objectives

Ten years ago, in the "Bega" University Clinic for Obstetrics and Gynecology of Timişoara, the bases were laid for the first Human Assisted Reproduction (HAR) Centre in Romania. Its creation was one of the recent achievements of medicine, if we take into account the fact that the first baby resulted from in Vitro Fertilization and Embryo – Transfer (FIV/ET) was born in England in 1978 (Edwards et al). Since then, thousands of babies are born every year as a result of this technique. The HAR Centre in Timişoara has had results similar to those of the largest centers in the world.

In the center data base there is a significant number of parameters, such as: causes of infertility (which led to the HAR's decision), specific investigation means to determine the women or couples which can benefit from this technique, fertility rate, pregnancy rate, etc. These date do not form the subject of the present study, but they can be included globally as guide mark.

Globally analyzed, the obstetrical pathology of the mother who turned to the HAR is significantly more charged with spontaneous or provoked miscarriages, as well as with one or two ectopic pregnancies. These accidents appear with a frequency of about 50%, explaining the primary or secondary tube sterility. The pathologic events of these cases interest more the reproduction organs and in a lower measure the other systems and organs (especially the endocrine system) with impact upon the reproduction function.

For a long time the woman's sterility was believed to guide a couple towards the HAR. Nowadays it is admitted that the masculine sterility is a very frequent reality which can determine a couple to make a FIV/ET.

All the mentioned data are important to obtain a pregnancy, after one or more previous experienced resulting in reproductive failure. They interest particularly the following fields: embryology-genetics, gynecologic endocrinology and obstetrics gynecology; these specialists realize the team of a HAR center and are permanently preoccupied by the optimization of the technologies leading to an ever higher pregnancy rate (the percentage ratio of the number of pregnancies obtained and the number of FIV/ET realized).

Concerning the perinatal period, the birthrate for HAR babies seems very important. For neonatology the "take home baby" rate is very important, that is the number of newborns integrated in their families as to the total number of births resulting from HAR, compared to the newborns resulting from natural reproduction (RN).

The HAR methods offer to a couple labeled as "sterile" the chance to have a baby. Once the pregnancy installed, its evolution does not differ from a Natural Reproduction (NR) pregnancy, being exposed to the same risks. The significant difference is the higher number of multiple pregnancies (double or triple) in HAR, as a consequence to the present FIV/ET techniques.

Thus, in order to increase the pregnancy chances to obtain a unique pregnancy, ET is performed with a number of 3 – 6 embryos. In such conditions the probability to obtain a twin (double or triple) pregnancy increases. The continuous improvement of the HAR techniques allows the performance of ET with a single embryo, but reduces the chances of pregnancy.

Coming back to the results of the HAR Centre in Timişoara, up to now the "take home babies" rate has been over 500 babies, adding up all the centers in Romania where babies resulted from HAR were born. Out of these, only 109 were born in the "Bega" University Clinic.

The objective of the research is the analysis of physical and functional parameters as well as of adaptation issues and precocious neonatal pathology in the group of newborns resulting from HAR, compared to a control group representing newborns resulted from NR which followed a HAR birth. Together with the above mentioned parameters, certain essential perinatal data were selected as comparison landmarks between the two groups.

Material And Method

The studying material is represented by a group of 109 HAR resulted newborns at the FIV/ET Center of the "Bega" Clinic and a comparable group of 95 NR resulted newborns at the same center selected following the case-control study pattern, that is after the birth of a HAR baby and included in the study group, the following newborn resulting from NR was included in the control group (table I).

Table I. The study lot. Cases distribution using year's study

Year's study	Nr. of the birth	Nr. de newborns	Twins Double	Twins Triple
1995-1996	4	4	-	-
1996-1997	7	7	-	-
1997-1998	8	8	-	-
1998-1999	10	10	-	-
1999-2000	11	11	-	-
2000-2001	10	13	1	1
2001-2002	10	10	-	-
2002-2003	10	13	1	1
2003 - 2004	13	17	4	-
2004 -2005	12	16	2	1
Total	**95**	**109**	**8**	**3**

The difference in numbers between the groups results from the fact that in the study group there were five twin pregnancies (two double and three triple), whereas in the control group there were only single pregnancies. In all the cases included in the study the significant parameters for comparison according to the study pattern were followed:

- mother's age;
- pregestation ± gestation maternal pathology;
- gesta – para categories;
- birth modality (± birth incidents);
- gestation age (newborn category);
- anthropometric indices (newborn category);
- special newborn categories ("high" prematurity, twin);
- immediate neonatal adaptation (APGAR score);
- neonatal adaptation issues: initial weight loss, neonatal jaundice, metabolic adaptation, etc.;
- feeding initiation and continuation;
- share of breastfeeding during the first 72 hours;
- release from hospital and integration in the family; average hospitalization;
- cost – efficiency ratio;
- medical follow-up, evolution, prognostic;
- subsequent social insertion.

These parameters were considered important for the comparative analysis and, they were illustrated and discussed.

At the primary analysis of the cases we did not register important differences concerning the sex, area or source distribution. As to the social-economical and cultural level, it is clearly favorable to the study group, since HAR represents an expensive medical procedure, and the insurance system in our country does not cover for it. We did not register significant differences between the groups regarding the gestation pathology either; as to the preexisting parental pathology, the significant difference in the study group is given by the pathology of the genital system which led the couple to choosing FIV/ET.

Results and Discussions

Significant differences between the two groups were registered referring to the mother's age (Table II). Almost half of the mothers in the study group range in the risk group (36 – 40 years old) or even of very high risk (over 40 years of age). By comparison, in the control group there is a "normal" distribution of the mother's age, similar to the general population for the NR.

Table II. Cases distribution using mother's age

Age (years)	≤ 20	21-30	31-35	36-40	> 40	Total
Study lot	-	23	39	23	10	95
Control lot	8	57	20	9	1	95

Generally, the couples who turn to HAR do it after failing several times in biological reproduction trials, finally accepting (sometimes at a "risk" age) the HAR techniques as a last chance of having a child.

The mentioned aspect is largely found in the distribution of the cases according to the obstetrical past of the mother (Table III).

Table III. Cases distribution using the obstetrical mother's past

Gesta/Para	GIPI	GIIPI	GIIIPI	G>IIIPI	GIIPII	GIIIPII	GIIIPIII	G>IIIP>III	Total
Study lot	49	7	9	24	6	-	-	-	95
Control lot	16	15	7	4	27	4	8	14	95

The study group is significantly dominated by primiparous women and multiparous women. By comparison, in the control group there is a balanced distribution of the gesta/para category.

In the primiparous category in the study group are included the women at the first gestation experience irrespective of the biological age and who, besides HAR, presented a previous reproductive failure. This category is significantly dominant (over 50%) and represents an argument concerning the correct indication for the HAR.

The other cases of the study group (the multiparous/primiparous category) experienced partial failures in reproduction since previous pregnancies concluded in abortions, which motivated them to accept the HAR techniques (after a severe "inventory" of the causes leading to reproductive failure).

Due to its high cost, a pregnancy resulting from HAR is more severely followed and monitored, and the pregnant women attend rigorous prenatal checking.

By comparison, in the control group, only primiparous or secundiparous mothers seem more motivated to attend rigorous follow-up of the pregnancy. Prenatal checking, periodical investigations, early detection of certain diseases during the pregnancy and their treatment of prophylaxis are more rarely or infrequently recorded in the cases of the control group (mostly in the multiparous category). Nevertheless, we have not registered significant differences between the two groups concerning the primary gestation or pregnancy induced pathology.

We have also registered eleven twin pregnancies in the study group (eight double and three triple), which represents 11,57%, by comparison, in the control group we have not registered any twin pregnancy.

The way of giving birth represents a significant difference compared to the control group.

The high risk as well as the higher frequency of risk age in the mother and the need of an increased protection of the fetus, leads to the significant increase of the cesarean operation births in the study group. The high frequency of prematurity, twin pregnancies and low weight at birth in the HAR cases are also adding up.

The distribution of the cases according to the gestation age and birth weight (fig. 1 and 2) shows clearly this difference.

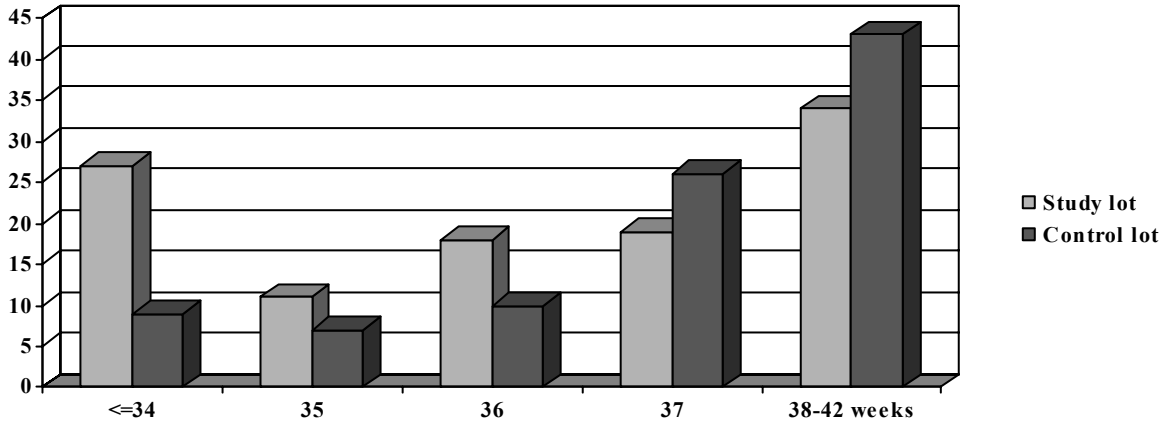

Fig. 1: Cases distribution using gestational age (weeks).

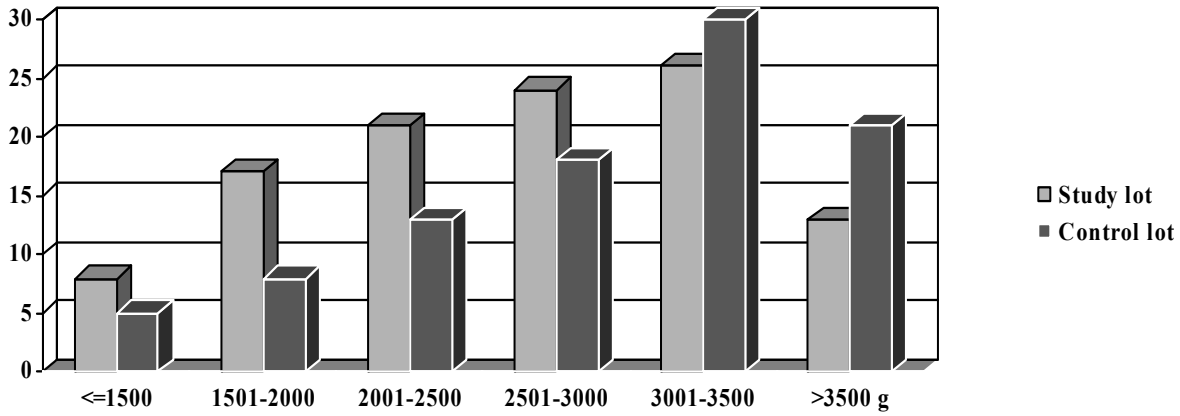

Fig. 2. Cases distribution using birth weight (g).

Thus, in the study group, a significant percentage of newborn have a gestation age ≤ 36 weeks and a birth weight ≤ 2500g.

By comparison, in the control group, the frequency of these categories is significantly lower.

The issues mentioned for the study group are also reflected in the immediate neonatal adaptation, shown by the APGAR score at birth (fig. 3).

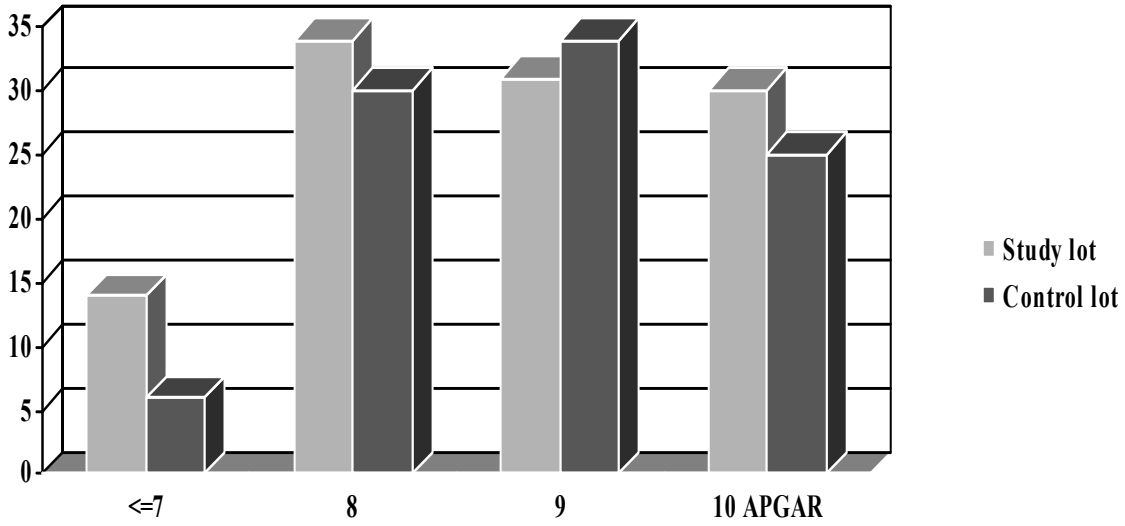

Fig. 3. Cases distribution using APGAR score at birth.

Irrespective of all the precaution measures and the higher anticipation degree of birth problems, the APGAR quotation is much better in the cases of the control group. This fact is greatly due to the higher frequency of caesarian births in the cases of the study group; in most situations it comes to an iterative caesarian, without labour and without immediate adaptation reaction caused by the "catecholaminic wave" which accompanies the natural birth. In such conditions, the adaptation of the newborn extracted by caesarian is often more difficult due to the slower resorption of the bronchial-pulmonary liquid. But in a global analysis there are no important differences between the two groups, both in immediate adaptation and during the first days of life.

In the figures 4 and 5 we quantified and compared two major problems of the precocious neonatal period, the initial weight loss (% as to the birth weight) and the duration of the neonatal jaundice (days) respectively.

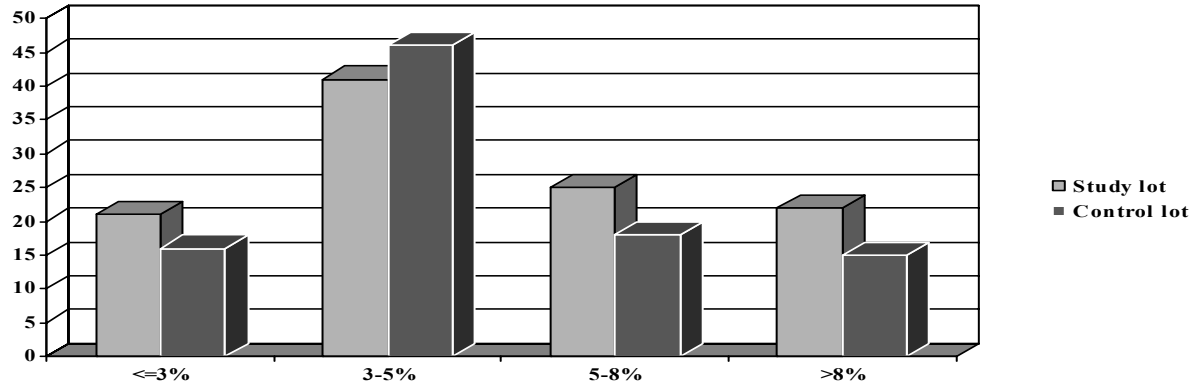

Fig. 4. Cases distribution using the initial weight dimination (% against the birth weight).

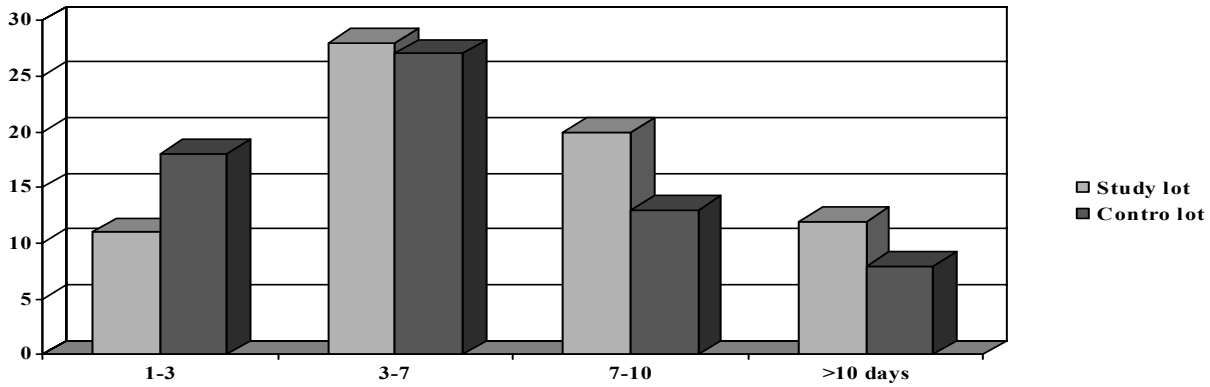

Fig. 5. Cases distribution using the jaundice's length (days).

Top be noticed that both the intensity (proportion) of the initial weight loss and the duration of the jaundice are significantly higher in the cases of the study group. This can be largely explained by the higher frequency of prematurity and twin pregnancies in the HAR cases by comparison to the NR cases.

An important parameter followed in the study was the initiation of feeding in the neonatal period and the share of the natural feeding. Therefore, in our clinic the modern concept of early initiation of natural feeding in healthy newborns (during the first 3 – 6 hours of life) and of the early enteric feeding in any category of newborns (including small premature babies), irrespective of the kind of feeding, but using human milk as much as possible has the precedence.

We have analyzed comparatively the age of initiation and the share of breast feeding during the first 72 hours of life in the two groups (fig. 6).

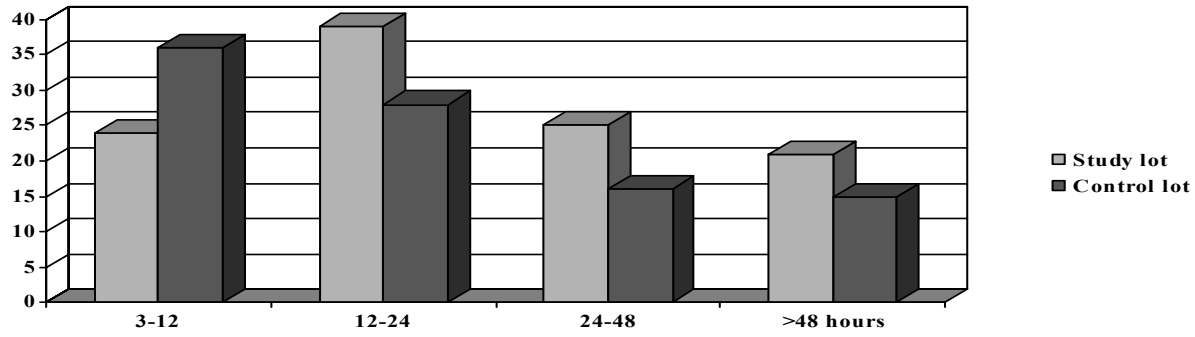

Fig. 6. Cases distribution using the age of nourishment originating (hours).

We have found in both parameters a sensible and significant superiority of the cases resulting from NR and a higher flexibility in initiating and continuing postnatal feeding. The explanation is found in the higher frequency of prematurity (later initiation of feeding) and higher frequency of caesarian births (later initiation of lactation) in the cased derived from HAR as compared to those derived from NR.

By continuing the research of the parameters taken into account, we registered a significant difference concerning the average hospitalization period and the duration of medical care given in the neonatology department. This parameter represented 10.7 days for the HAR resulting newborns compared to 5.6 days for the NR resulting newborns. According to this result the cost of postnatal care are much higher in the first category.

As to the morbidity during the neonatal period, there were no differenced registered between the two groups, all the cases being integrated in their families after the initial recovery. No death was registered in the cases studied and followed up.

Their evolution was good and they all range between the optimal parameters of neuron-psychomotor and physical development according to the biological age. The medical follow-up showed a more frequent and stronger psycho-affective and especially social protection in the newborns and children resulting from HAR, who benefit from better social and economical conditions as compared to those resulting from NR.

Conclusions

1. RUA represents a real victory for medicine against sterility. Because of its results, HAR Center of Universitary "Bega" Clinic from Timişoara, is registered in the circle of the greatest profile around the world**.**

2. The evidence, the pursuit and the monitorization of pregnancies and births which became from HAR, with a better anticipation and preventing maternophetal pathology problems, occure now advantageously and having better results comparatively with the previous pregnancies and natural births.

3. The high risk degree, and also the important prematurity and twins frequency explain the high frequency of caesarian birth at HAR cases; we add here the mother's age risk, semnificatively increased at the study lot.

4. There is an prematurity proportion, fetus hipotrophy and twins to the cases which became from HAR. Starting from this reality, there are some important differences between the two lots, as you can see:

→ the newborns became from HAR present an important frequency of neonatal adaptation and they need special nursing in the intensive therapy unit ;

→ initial decrease balance is bigger, and the initiating of nourishment is bees realizing later at the newborns which became from HAR; in the same time, the breast nourishment balance in the first 72 hours is significant low at this category vis a vis of newborns resulted from NR;

→ there are not significant differences about the intensity and the duration of newborn icterus at the two lots;

→ important differences appear concerning the average hospitalization duration period: 10,7 days for the newborns resulted from HAR instead of 5,6 days at the newborns resulted from NR; in key with this postnatal nursing costs are higher than the first category.

5. The study results underline that after birth, the biological child's evolution in mostly independent of the modality of conception and more dependent of the neonatal fetus status in the perinatal period. So psycho - affective and social protection seems to be more important for the newborns resulted from HAR.

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III. PEDIATRICS

PHYSIOTHERAPY IN CYSTIC FIBROSIS IN SCHOOL CHILDREN AND TEENAGERS

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Summary

The purpose of the study was to compare the efficiency of different technique of clearance in cystic fibrosis. The lot of study consisted of 12 children from the records of the Cystic Fibrosis Centre Timisoara. The methods of clearance were: active cycle of respiratory technique and flutter – therapy. Conclusions: both tehchnique have the same efficiency, a consequent and correct physiotherapy is probably the most important factor in the prevention of a chronic pulmonary infection.

Key words: cystic fibrosis, physiotherapy, children

The premises of the study

Cystic fibrosis (CF) is the most frequent monogenic disease, autosomally recessive, with chronic evolution, progressive, lethal potential of the white population. CF is characterized by a clinical polymorphism, but the pulmonary involvement represents the decisive prognosis element. That is why the physiotherapy of the respiratory apparatus is a compulsory part in the management of the sick with CF. Physiotherapy allows the clearance of the respiratory channels and implicitly prevents the bacterial infection. The physiotherapeutic techniques are individualized according to age, the compliance of the sick person and the experience of the physiotherapist (2,3).

The purpose of the study

The purpose of the study was to compare the efficiency of some of the classical techniques of respiratory clearance (the active cycle of respiratory techniques – ACRT) with some newer techniques, flutter-therapy respectively (expiratory pressure positive oscillating).

Material and method

The study was performed between january 2003 – june 2004

The lot of study consisted of 12 children from the records of the Cystic Fibrosis Centre Timisoara (8 girls and 4 boys) with an age range between 8 and 18 years (average 12,4 years).

Depending on the applied techniques of physiotherapy, the lot was divided into two subgroups:

- gr. A: active cycle of respiratory technique (ACRT) carried out in various positions of postural drainage (fig.1, 2).
- gr. B:expiratory pressure positive oscillating (flutter – therapy) – fig.3.

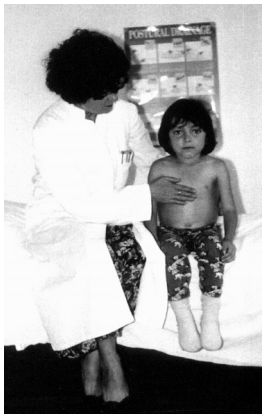

Fig. 1. Breathig control.
(phototeca of CF Centre Timisoara).

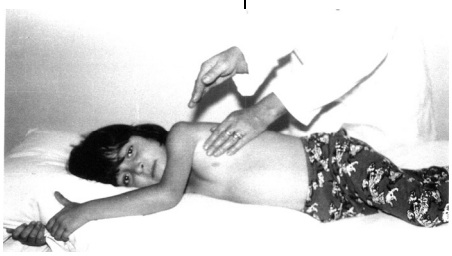

Fig. 2. Clapping in ACRT.
(phototeca of CF Centre Timisoara).

Fig. 3. Flutter therapy.
(phototeca of CF Centre Timisoara).

Followed parameters were: the character of the cough and of the phlegm and pulmonary physical signs; radiography and computer pulmonary tomography features; respiratory infection; nutritional status; respiratory functional tests (FVC, FEV1, FEF 25-75, FEV1 / FVC).

Results and Discussions

ACRT – mobilizes and eliminates the bronchial secretions in excess. It consists of: breathing control (RC), thoracic expansion exercises (TEE), the forced expiration technique (FET)

It can be applied in any position and it can be associated with the postural drainage. Between the various stages of the ACRT one can do percussions or tampotament and shake-ups (1,3).

Flutter-therapy combines the PEP technique (positive expiratory pressure) and therapy through oral oscillations of high frequency. It is done through a pocket device (Flutter VRP1). Flutter therapy improves ventilation and makes respiration easier (4,5,6).

At group A

The clinical and paraclinical data before physiotherapy were: general clinical state relatively good, productive cough in all children, the aspect of the phlegm suggestive for the isolated germ, constant and significant radiological modifications for CF (emphysema, mucus bronchogram etc.). Bronchiectasis were present in 5 children (through computer tomography – CT). Five out of the six have been infected (*Staphylococcus aureus* or *Pseudomonas aeruginosa*). The nutritional status was good in most of them. Ventilation functional tests were modified in 4 children.

After physiotherapy we observed: change in the characteristics of the cough (decrease up to disappearance), the aspect of the phlegm (in those for which the cough has remained the phlegm has become more fluid and clearer). Radiological and CT signs: were maintained for bronchiectasis but did not progress. was The persistence of the infection with *Pseudomonas* and the infection with *Staphylococcus* in one child. The ventilation functional tests have shown the increase of the quantified parameters (fig. 4)

Note: In the treatment of bacteria pulmonary infection, physiotherapy was dubbed by specific antibiotherapy.

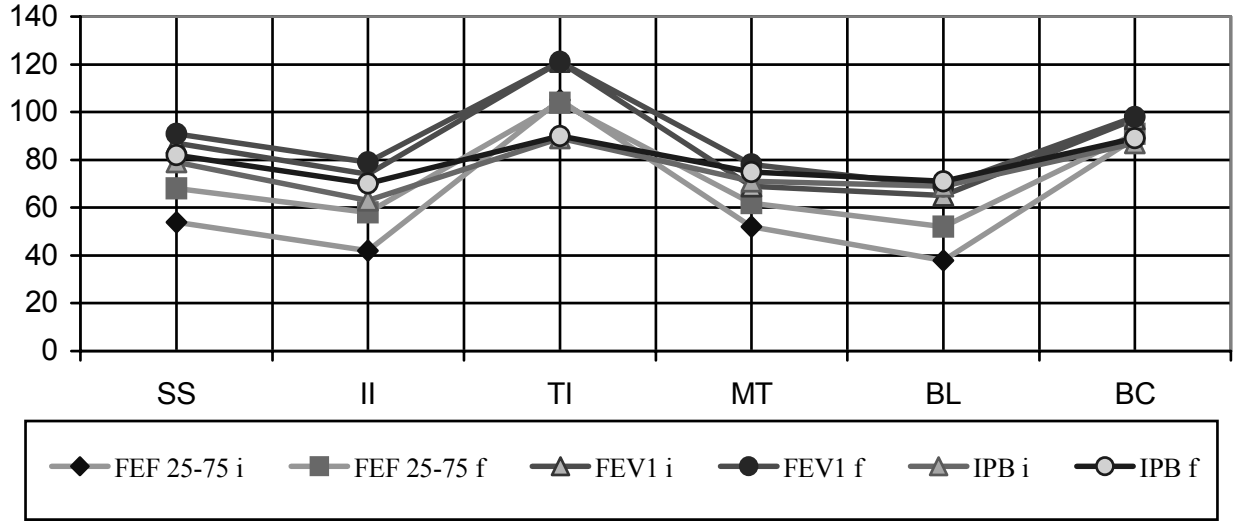

Fig. 4. The comparative values of the basal ventilometric indices before and after physiotherapy in group A.

At group B

The clinical and paraclinical data before physiotherapy were: most children with hyperinflation, increased dorsal cyphosis, clubbing, greenish productive cough, abundant in children infected with *Pseudomonas aeruginosa*. Bronchiectasis were present in 5 children. Three out of 6 were infected with *Pseudomonas aeruginosa* and 2 with S*taphylococcus aureus.* About status nutritiona, two children have shown a severe growing failure. The ventilation functional tests were modified in all children.

After physiotherapy we observed: the significant improvement of the general clinical state decrease of coughing, change in the feature of the cough, clearer and more fluid, but with the persistence of the infection with *Pseudomonas* in those with chronic infection. Nutritional status was good in 4 children, in one of them it has improved, and in another one the severe decrease in growing was maintained. The ventilation functional tests have shown the significant improvement of all the evaluated ventilometric indices (fig. 5).

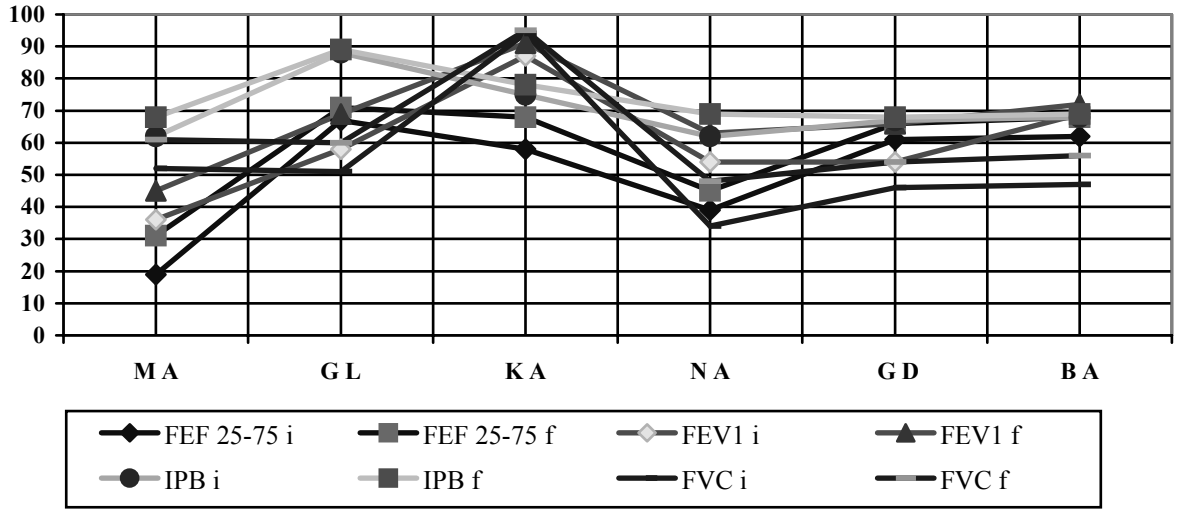

Fig. 5. The evaluation of the respiratory functional modifications before and after physiotherapy in group B.

Conclusions

At school age and teenage years the classical clearance techniques (ACRT) as well as the newest ones (Flutter-therapy) are equally indicated, they are both efficient, but the cost and accessibility to flutter may be an impediment in choosing this variant

Physiotherapy must be included in the management program of any person with cystic fibrosis, it has to start immediately after diagnosis and must be performed daily both when there are increases in infections, or lack of them, when the number of sessions increases.

A consequent and correct physiotherapy is probably the most important factor in the prevention of a chronic pulmonary infection and when added to antibiotics therapy it helps to the significant improvement of the prognosis and the maintenance of a quality of life as close to normal as possible.

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BENIGNE ARRHYTHMIAS IN SCHOOLCHILDREN

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Abstract

Children arrhythmias may be transient or permanent, congenital or acquired (rheumatic fever, myocarditis), caused by a toxin, drugs, or be a sequel of surgical correction of congenital heart disease. The major risks of any arrhythmia are those of severe tachycardia or bradycardia leading to decreased cardiac output, or the risk of degeneration into a more severe situation, for example, ventricular fibrillation. One of the major issues in the management is to determine whether the rhythm disturbance is prone to deteriorate into a life-threatening tachyarrhythmia or bradyarrhythmia. Some rhythm abnormalities, such as single premature atrial and ventricular beats, are common among children without heart disease and in the great majority of instances do not pose a risk to the patient.

Key words: arrhythmias, sudden death

Introduction

Not all arrhythmias occur in a symptomatic context in small children. But in older patients usually a rhythm disturbance associates several symptoms that can alert the parents or the teachers and lead to further investigations. Sometimes symptoms are overwhelming the child, producing a wide distress to the audience. Unfortunately there are situations when without any warning an arrhythmia strikes and ends in sudden death, more often during exercise in a sport class. This is the main reason why we performed this study, among children, mainly from the neighborhood schools. Fortunately, during the 4 year period of this study, we did not experienced any life threatening situations among this children, although we manage to discover some conditions that could led in the future t such events.

Purpose

The aim of this paper is to check the incidence and occurrence of arrhythmias in a group of 500 school children from Timisoara, including a high school with sport profile.

Material and method

The study has been performed during a 4 years period from 2001 to 2004. The group of patients consisted of 500 school children aged between 7 and 18 years, outpatients of the pediatric ambulatory of the Clinical County Hospital Timisoara. This was a randomized lot of patients, with poor or lack of symptomatology, submitted to a routine control prior to sport classes in order to discover no symptomatic cardiac diseases.

The initial evaluation of each scholar began with a careful history, specifically questioning the patient regarding the presence of palpitations, syncope, chest pain, or other symptoms. We also inquired about any circumstances that can trigger an arrhythmia, such as emotionally upsetting events, ingestion of caffeine-containing beverages, cigarette smoking, exercise, or gastrointestinal problems. Family history can be helpful because a variety of familial disorders can result in arrhythmias, including myotonic dystrophy, Duchenne muscular dystrophy and hypertrophic cardiomyopathy

The physical examination was complete, insisting on the cardiovascular system. This included the blood pressure measurement in orthostatic and sitting positions.

Regardless of previous findings, each child was investigated recording a 12-lead electrocardiogram (EKG). The investigation was completed by echocardiography, biological explorations, exercise stress testing and a 24 hours Holter monitoring in particular cases in order to discover an underlying cardiac disease. This last part of the evaluation was mostly performed in Clinic II Pediatrics, the children being hospitalized for 2-5 days.

Results

Sex distribution of the children

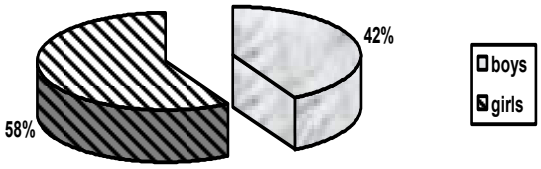

Fig.1. Sex distribution

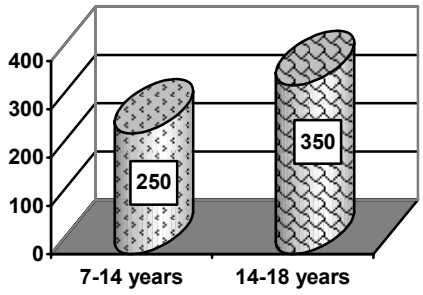

Fig.2 Age distribution

From all 500 school children 370 had no cardiac disease or electric disturbances at the moment of the examination. In 130 cases we noticed EKG modifications, associated or not with a positive history and/or clinical findings, as shown in the following table. We mention that the percentage refers to the total of 500 children investigated and that sometimes more than one of the EKG anomalies were found in some cases.

Table 1. EKG anomalies

Arrhythmia	Nr cases	%
Sinus bradycardia	52	10,4
Sinus tachycardia	37	7,4
Atrial parasystolia	18	3,2
Premature atrial beats	14	2,8
Premature atrioventricle complexes	3	0,6
Wolf-Parkinson-White syndrome	4	0,8
Lown-Ganon-Levine syndrome	3	0,6
Premature ventricle beats	34	6,8
Ventricular tachycardia	3	0,6
Heart blocks	44	8.8
Repolarization anomalies	67	13,4

In order to perform a more accurate evaluation of arrhythmias and cardiac or noncardiac underlying conditions, we hospitalized 42 patients in Clinic II Pediatrics. Further exploration included blood chemistry, chest X-ray, echocardiography, repeated EKG, exercise stress testing and Holter monitoring.

Consecutive investigations leaded to the discovery of different situations, as presented in Table 2. We also have to mention that several patients associated more than one pathologic condition.

Table 2. Specific diseases

Diagnosed disease	Nr. Cases	%
Atrial Septal Defect	3	0,6
Ventricular Septal Defect	10	2
Hypertrophic cardiomyopathy	6	1,2
Dilated cardiomyopathy	2	0,4
Mitral valve prolapse	45	9
Streptococcical infection	15	3
Preexcitation syndromes	4	0,8

Atrial parasystolia	22	4,4
Isolated heart blocks	17	3,4
Orthostatic hypotension	35	7
Systemic hypertension	12	2,4
Hypocalcaemia	65	13
Food disorders	25	5

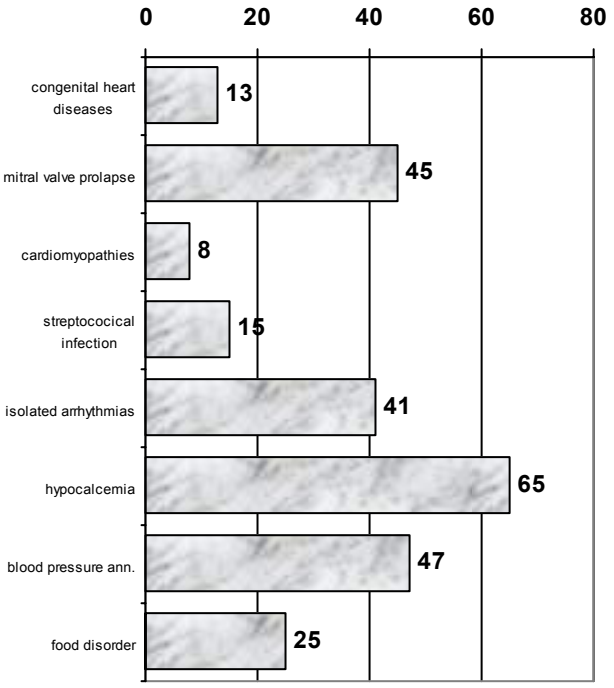

Fig.3 Repartition of specific diseases underlying the arrhythmias

Holter monitoring was a valuable method to investigate higher risk patients regarding the occurrence and frequency of cardiac rhythm disturbances. Unfortunately, we still need more devices, in order to make a more precise evaluation of the patients with sever cardiac diseases, like cardiomyopathies, to extend the monitoring period at home, in a normal life situation. This is the only way to ensure a lower rate of sudden death due to arrhythmias because we can adjust the treatment and life regime indications to individual conditions.

Discussions and conclusions

The availability of an increasing number of diagnostic and therapeutic technologies, coupled with concerns over the rising costs of health care, has generated growing interest in determining the cost and effectiveness of cardiological care. But not the cost of a patient should be our first concern, because we are dealing with children. Every situation that can lead to an accident or incident threatening the life of a child is a matter of importance. Unexpected sudden death is a tragedy at any age but is particularly so in childhood and adolescence. The causes of sudden death in childhood are known but their relative importance is difficult to assess.

Although in our schools few incidences occurred concerning sudden death in children in the last decade, it is important to discover from the very stages of evolution cardiac diseases that can induce dangerous arrhythmias. Physical exercise but also intellectual stress in school children can start a life-threatening rhythm disturbance. The economical conditions does not support schools with medical and human personal trained to deal with emergency cardiac situations.

We noticed that in our lot of study 13 patients "escaped" until this age of being diagnosed with a congenital heart disease. This proves that in our health system many things can be improved, especially the collaboration between the family doctor and the policlinic or hospital specialist physician. There still are patients of different ages with congenital heart anomalies undiagnosed. That is why our research will continue the following years, in order to low as much as possible the risk of life threatening situations, especially of cardiac etiology.

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CANCER RISK OF HELICOBACTER PYLORI INFECTION IN CHILDREN

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Summary:
Helicobacter pylori represents one of the most common and medically proeminent infections worldwide. Helicobacter pylori has been highlighted as an agent with an important role in gastric carcinogenesis. This action is due to morphopathological changes of the stomach as well as to bacterial virulence factors.
Key words: gastric cancer, Helicobacter pylori, children.

Helicobacter pylori can be considered as a health-care issue because of the mortality associated with the infection, owing to the risk of bleeding ulcers and gastric cancer. Infection with Helicobacter pylori can result in the development of gastritis in all infected humans, including children and adolescents (1).

Helicobacter pylori infection seems to be associated with an increased risk of developing gastric cancer. However, only a small number of infected individuals will develop gastric cancer (2), including mucosa-associated lymphoid tissue lymphoma and adenocarcinoma (3).

The infection is contracted primarly in childhood and infection from childhood appears to enhance the risk for carcinogenesis.

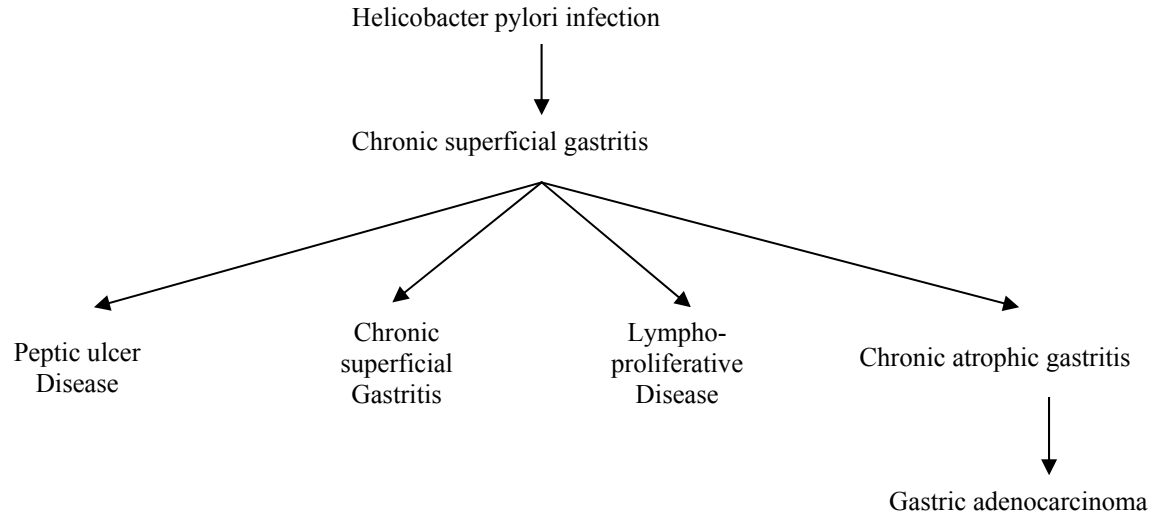
In 1994 Helicobacter pylori was classified as a group 1 carcinogen for gastric cancer by the International Agency for Research on Cancer.

Adenocarcinomas are the most common malignant tumors of the stomach comprising 97% of all gastric cancers with the remaining 3% being lymphomas or leiomyosarcomas. Infection with Helicobacter pylori has not been associated with proximal gastric carcinoma.

The strongest epidemiology evidence linking Helicobacter pylori infection with gastric cancer comes from 3 nested case-control studies published in 1991. These studies using stored serum demonstrated that Helicobacter pylori infected people are more likely to develop gastric cancer.

Case-control studies based on serologic evidence of infection may underestimate the association between Helicobacter pylori and gastric cancer because Helicobacter pylori colonization of the gastric mucosa decreased in association with the development of gastric atrophy.

The colonization with Helicobacter pylori determine the development of gastric atrophy, also called multifocal atrophic gastritis. This involves loss of gastric mucosal glands and hence altered gastric secretion. The evolution of gastric atrophy may be the first step towards the development of gastric cancer. This lesion might then lead to further changes, among them intestinal metaplasia and dysplasia, conditions that typically precede cancer (4).



It has been proposed that specific bacterial virulence factors may play a role in the development of gastric cancer. Strains of Helicobacter pylori can be differentiated based on whether they contain the cytotoxin associated gene (cag).

The cagA gene codes for the Cag-A protein, which seems to stimulate the production of chemotactic factors for the neutrophils by the gastric epithelium of the host. A certain portion of Helicobacter strains (40%), by unexplained causes, does not produce this protein.

Cag is a marker for the presence of a pathogenicity island in the Helicobacter pylori genome and may be a marker for a more virulent type of Helicobacter pylori.

Later research indicated that people infected with Helicobacter pylori strins bearing the cagA gene have a higher risk of acquiring peptic ulcer disease or stomach cancer than people with strains lacking the gene.

We know now that cagA is a part of a region in the Helicobacter pylori chromosome that also contains genes encoding proteins that form a type IV secretion system (TFSS). Bacterial cells assemble these systems to export large, complex molecules into host cells. Several of the Helicobacter pylori genes near cagA encode TFSS proteins that assemble into a structure analogous to a miniature hypodermic needle. This structure injects the CagA protein into the epithelial cells that line the human stomach.

After cagA enters an epithelial cell, enzymes in the host chemically transform the protein, allowing it to interact to several humans protein. These interactions ultimately affect the cell's shape, secretion and signals to other cells. Strains of Helicobacter pylori bearing the cagA gene cause more severe inflammation and tissue injury in the stomach lining than do the strains without the gene. These differences may explain the increased disease risk in people carrying the cagA strains.

After the exposure to cagA positive Helicobacter pylori strains, an increase has been reported in catalase, glutathione peroxidase, and superoxide dismutase activity. This increase is associated with fewer DNA adducts and reduced susceptibility of the gastric cells to the irreversible injuries from reactive oxygen species (ROS) compared with exposure to cagA negative strains. Such alterations of the ROS scavenging enzymes may partly account for the increased risk of gastric cancer in individuals with Helicobacter pylori infection.

There are some Helicobacter pylori strains that caused large holes, called vacuoles, to form in epithelial cells in culture. The active agent was a toxin, dubbed VacA, encoded by a gene that is named vacA. In addition to forming the vacuoles, VacA turns off the infection-fighting white blood cells in the stomach, diminishing the immune response to Helicobacter pylori. Unlike cagA, vacA is present in every Helicobacter pylori strain, but because the gene's sequence varies substantilly, only some of the strains produce a fully functional toxin. John C. Artherton found four major variations in vacA: two (m1 and m2) in the middle region of the gene and two (s1 and s2) in the region that encodes the protein's signal sequence, which enables the protein to move through cell membranes. Helicobacter pylori strains with both m1 and s1 variations produce the most damaging form of the VacA toxin (5).

It has been observed that a higher number of antigenic proteins can be detected by immunoblotting among controls than among gastric cancer cases. Immunoblotting has also been shown to be both a more sensitive and a more specific detection method for Helicobacter pylori infection than enzyme immunoassay, EIA. The combination of antibodies towards the VacA and CagA protein is associated with an increased risk of gastric adenocarcinoma, and subjects infected with strains expressing the CagA protein have a higher risk of gastirc cancer. In a study reported by swedish researchers in 2002, antibodies towards the CagA protein and towards p30 (UreA) were associated with an increased cancer risk. This observation is consistent with a particulary strong link between infection with CagA positive Helicobacter pylori strains and risk of gastric cancer (6).

The severity of gastritis associated with Helicobacter pylori infection was correlated with mucosal expression of tumor necrosis factor alpha subunit and IFN-gamma. The robustness of the mucosal Th1 response has been associated with progression to atrophic gastritis and gastric cancer, as supported by animal models (7).

There is a evidence suggesting an association between Helicobacter pylori infection, which is almost always acquired in childhood, and gastric cancer occuring in adulthood. This association is specific to gastric cancer occuring distal to the cardia. However, we have to remember that only aproximative 15 of Helicobacter pylori – infected children will develop gastric cancer. Furthermore, infection alone may not be sufficient to cause cancer, and a number of others factors have been associated with an increased risk of gastric cancer. These include blood group A, poor dietary intake of vitamin C or carotenoids, as well as increased intake of salted and smoked foods. Whether the eradication of Helicobacter pylori can prevent the development of a significant number of cases of gastric cancer despite the persistence of other risk factors remains unknown.

Although definitive studies on the role of Helicobacter pylori in gastric cancer may therefore never be achived, or will at least take many years to carry out, a consensus as to the significance of Helicobacter pylori infection in childhood in relation to the risk of gastric cancer is urgently required. The major question that arises for clinicians is how to respond to H pylori infection when it is identified at endoscopy or by noninvasive methods such as 13C-urea breath testing. A decision to treat all infected children to reduce their risk of developing gastirc cancer implies that community screening for this infection in childhood should be undertaken to identify and treat all infected children. Nevertheless, parents of children undergoing investigation will have to be informed when this infection is identified. The recent findings of Brenner et al and El-Omar et al (2) suggest that we should treat infected children who have a family history of gastric cancer.

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BONE MINERAL DENSITY IN CHILDREN WITH GROWTH HORMONE DEFICIENCY TREATED WITH RECOMBINANT HUMAN GH

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Abstract

It is known that growth hormone deficit (GHD) in children is associated with decreased bone mineral density and improves with substitutive treatment.The aim of the present paper was to evaluate bone mineral density BMD in GHD children treated with rhGH. The studied lot included 45 children with GHD treated with growth hormone, followed-up in Clinic II Pediatrics between 1997-2004.
Our results are concordant with the literature data showing that BMD is decreased in GHD children and rhGH improves BMD after the first year of treatment.
Key words: Growth hormone deficit, bone mineral density, child.

Background

Data concerning bone markers in monitoring treatment with recombinant human growth hormone (rhGH) are still unclear. Although, numerous studies aim to establish a relationship between rhGH treatment and bone density in children. Beside its wellknown effects on linerar growth in childhood and adolescence, growth hormone exerts also, direct and indirect effects upon bone homeostasis and remodeling. Growth hormone deficit with childhood onset, influences not only linear growth but also bone mineral cumulation, so having, an important role in providing the proper bone density at each age (1).

The bone is an active tissue that is remodeling constantly, the old tissue being replaced by new tissue. In childhood and adolescence, the linear growth means also bone tissue cumulation, both through periostal aposition and growth plates calcification (2). Condrocytes are modulating the bone formation, the remodeling of preexistent mineralized tissue and also of the new bone, being specific in the growing child. Biochemical markers of the bone turnover (alkaline phosfatase, osteocalcin, urinary hydroxiproline, calciuria) are not specific to each process, in children, these markers being correlated also with growth velocity. Thus, these markers increase significantly in the accelerate growth periods, like the first year of life and puberty (2,3).

A significant cumulation of bone mass characterises mostly puberty and adolescence, when aproximately 25% of the total bone mass is achieved, thus, around the age 18, a percentage of 90 % of the peak bone mass (which is complete around the age 25-30) is attained (4). Bone turnover, is influenced by numerous local and general, nutritional and environmental factors, an important role being atributed to the hormonal factors.

From the dietary factors, an important role have calcium and protein intake and also vitamin D, which are essential for growth (5,6). The hormonal factors involved are GH and IGF1, thyroid hormones, glucocorticoids (before puberty) and sex steroids (in puberty and postpuberty). These are acting at different levels of the bone structures, corresponding to their specific bone receptors (fig. 1) (7).

On the other hand, experimental studies proved that exogenous glucocorticoids administration with a therapeutic aim, has a negative effect on the bone mass, inducing osteopenia, while the association of GH therapy is benefical, counteracting the negative effect of the glucocorticoids, through cortical bone mass cumulation (8,9).

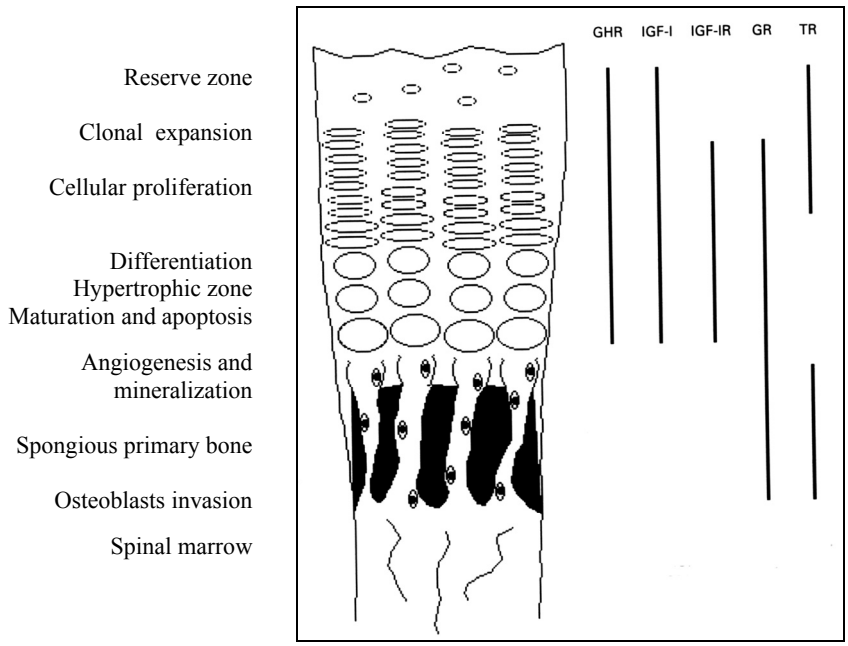
Material and method

The studied lot included 45 children with growh hormone deficiency (GHD), treated with rhGH folowed-up in Clinic II Pediatrics Timisoara between 1997-200. Children were aged between 3 – 15 years (mean age 10,5 ± 3,6), 29 male and 16 female (sex ratio 1,8). The diagnosis criteria for GHD included: height reduced for age (2 DS below the mean), slow height velocity (< 25th centile), delayed bone age, subnormal GH response at 2 provocative tests.

For the evaluation of bone mass density (BMD) we used the dual energy X ray absorbtiometry (DEXA) method in 21 children (aged over 12 years). Results were corelated with the alkaline phosphatse serum levels determined at every visit. In all cases serum calcium and magnesium were also measured.

Results and Discussions

DEXA evaluation showed lumbar osteoporosis and coxofemural osteopenia (fig. 2) in 10 cases (22 %), lumbar osteopenia in 6 cases (13,3%). BMD was normal in 5 cases (11,1%). (fig. 3). Of the 10 cases with lumbar osteoporosis, 2 cases were treated also with thyoid hormones (thyroxine), 4 cases were on plurihormonal therapy (thyroxine, corticoids, and sex steroids – in the last year of treatment) and 4 were in the first year of rhGH treatment, facts that could explain our findings.



Legend: GHR = GH receptor, IGF – IR = IGF1 receptor
GR = glucocorticoids receptor, TR = T3 receptor

Fig. nr. 1 – The action level of hormones in the bone (7).

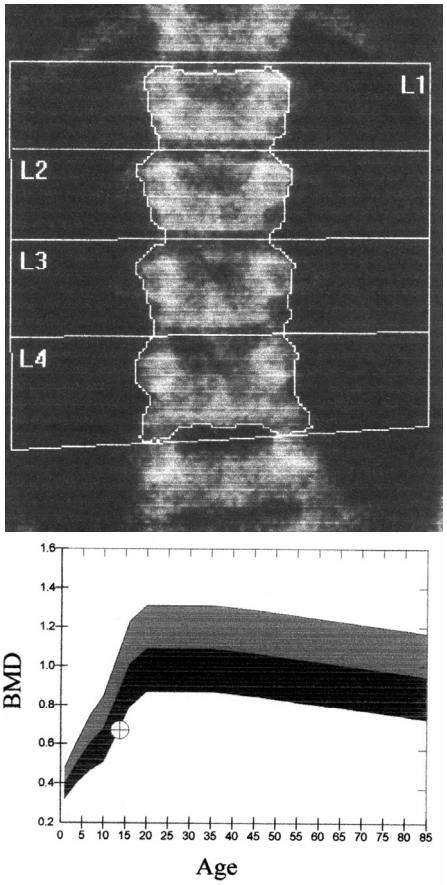


Fig. 2a. - Lumbar osteoporosis.

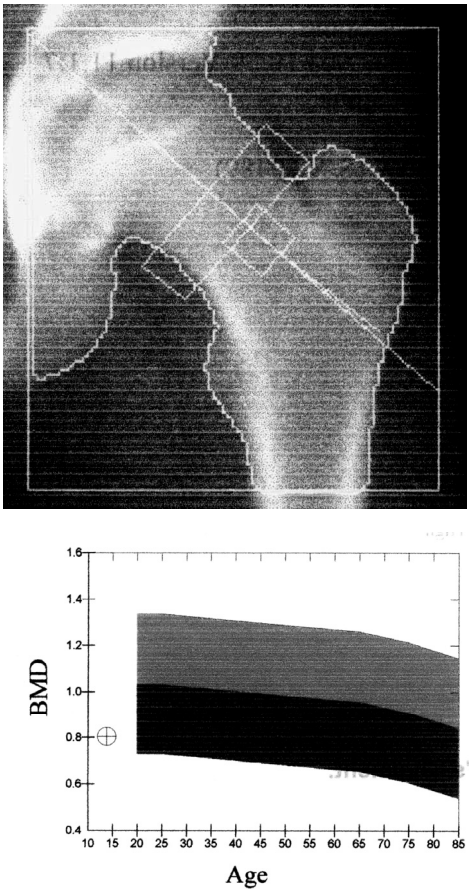


Fig. 2b. - Coxofemural osteopenia.

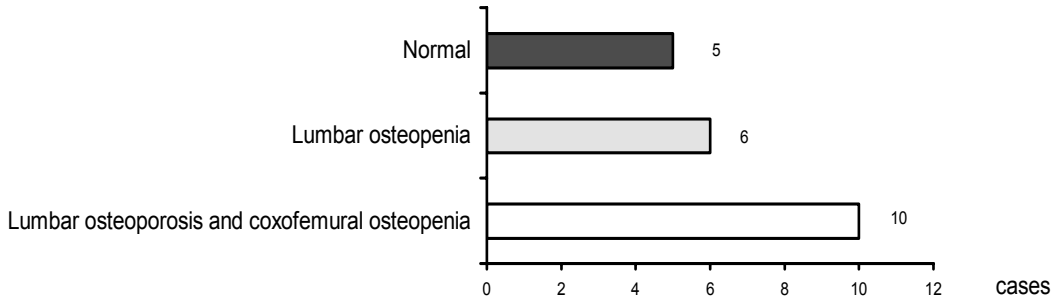


Fig. nr. 3 - Bone Mass Density evaluated by DEXA

Of the 6 patients with lumbar osteopenia, one received also treatment with L-Thyroxine, while 5 were in the second year of rhGH treatment.

Alkaline Phosphatase (APh), determined throughout the treatment period, showed an increase of the serum level above the cut-off normal level in 26 patients, after the first year of treatment (fig. 4), underlying the increase of the bone turnover, with the rhGH treatment. Moreover, in 14 of 26 patients the serum total and ionized calcium was decreased.

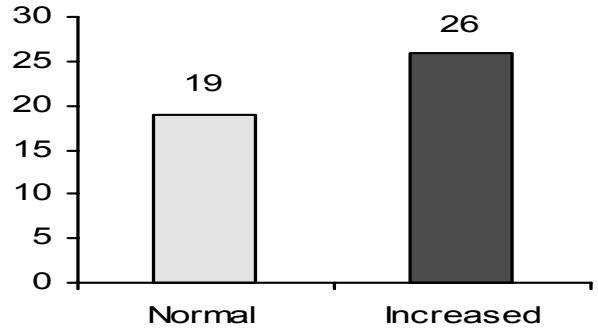


Fig. nr. 4 - Alkaline phosphatase after 1 year of rhGH treatment.

Considering the hypocalcemia and the increased APh, we supplemented the diet with calcium and D vitamin in all these patients. After two years of treatment, serum APh normalised in 15 of the 26 cases, remaining increased in 9 patients (fig. 5).

This aspect is corelating with the literature data, showing that after 6 months of rhGH therapy, bone density starts to recover, with an increase of the bone mineralization and, consecutively, of the bone density.

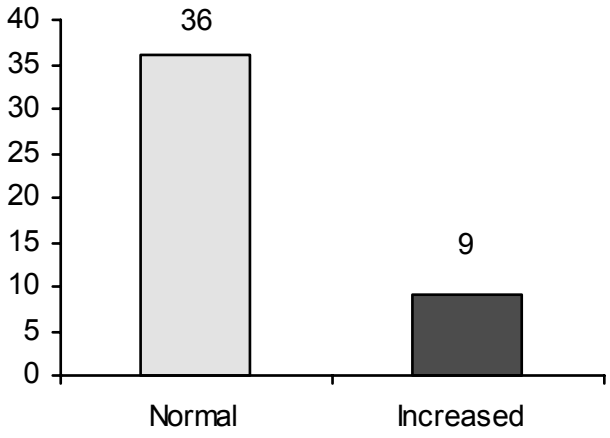


Fig. 5 - Alkaline phosphatase after 2 years of rhGH treatment.

These are still increased in the last year of treatment (at the time of DEXA evaluation) in the 4 cases with plurihormonal treatment (rhGH + thyroxine + corticoids + sex steroids) in whom the evaluation showed osteoporosis (fig. 6).

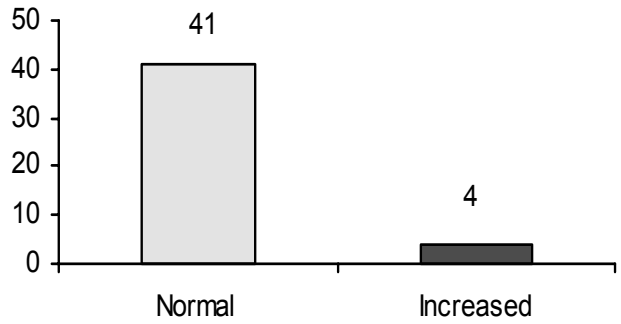


Fig. 6 - Alkaline phosphatase in the last year of rhGH treatment.

Our findings could be explained through many hypothesis. It is known that growth hormone deficit (GHD) in children is associated with decreased bone turnover and mineral density (10). Moreover, previous studies have proved that the initiation of growth hornmone therapy increases bone turnover and, in the same time, diminishes bone density in the first 6 months of treatment, reflecting the gap between the accelerated bone growth and the slower bone mineralization.

Bone turnover seems to be more accelerated in the trabecular than in the cortical bone, fact that explains the stadial correction of the bone density with the treatment, first in the vertebral bodies and only later in the whole body (11,12).

Previous studies have shown that in the first 6 months of treatment, bone density starts to improve, so that after 2 years of therapy, the bone density attains the normal parameters for age and height (12).

This favourable effect of the rhGH therapy on the bone mass, was proven in several studies, but it seems that, in patients receiving suboptimal doses of rhGH, bone density is decreased, before reaching the peak bone mass, sustaining the need of continuing rhGH therapy in these patients, even after attaining the final height, in order to obtain the correction of the bone density.

Worth mentioning that, with all the advantages of the hormonal therapy with rhGH, attainment of the peak bone mass, involves at first, a proper nutritional intake, especially regarding the calcium, D vitamin and protein intake.

D vitamin deficiency is frequent in the population from our country, both because of the weather (insufficient sunny season) and the lack of supplementation with D vitamin, and is responsible for a defficient bone mineralization in a significant number of healthy children and adults. This process will be accentuated in GHD children with or without treatment. In our patients the defficiency in D vitamin intake was associated with that regarding calcium supplements and a rational diet.

In the patients found with osteopenia, this might be explained through the associated effect of the therapy with rhGH, and, in one case, LT4, respectively. Moreover, worth mentioning that 4 of the patients with osteopenia were in the first 2 years of treatment, fact that permits the hypothesis of an insufficient period for the recovery of bone density with the substitutive treatment.

In the patients with osteoporosis, we consider that in the occurence of these modifications all hormonal factors were involved. Considering the unfavourable effect of corticotherapy on the bone density we consider that one of the determinant factors in the occurence of osteoporosis found in the 4 cases with plurihormonal substitution was represented by the association of glucocorticoids in the therapeutic scheme.

On the other hand, in these cases (all females) should be considered also the delayed puberty. It is wellknown the marqued effect of estrogens, at puberty, on the regulation, absorbtion and deposition of calcium in the bone, aiming to attain the optimal bone density and to prevent osteoporosis in adulthood. Moreover, we observed that the administration of low doses of estrogens in girls with hypogonadism determins a significant increase of the absorbtion and retention of calcium and also the decrease of calcium turnover in the whole body (13).

In the 4 cases with osteoporosis, considering the fact puberty was induced with some delay, aiming for a height gain as good as possible, before entering puberty, the lack of sex hormons and also the rapid growth induced by the rhGH treatment, would represent another explanation for the decrease of the bone density. Previous to the DEXA evaluation, the duration of estrogen therapy in these patients (few months), was not sufficient to exert a favourable effect on the bone mass.

We cannot get over the thyroid hormone therapy and their effect on the bones, having in view previous studies showing that under the circumstances of a substitutive long-term treatment, these hormones stress out the bone turnover, determining a decrease of the bone density, the effect being marqued more in the cortical than in the trabecular bone (14,15).

As a conclusion, we might say that bone modifications found in our patients, explained by the numerous factors involved, are concordant with the results reported by other authors showing a decreased bone density

in some GHD patients treated with rhGH comparatively with subjects of same chronological and bone age. Moreover, in these patients, bone turnover markers increase, attaining a peak at the end of the first year of treatment, decreasing than progresively and reaching the normal later (12,16,17), modification observed also in our patients.

Conclusions

1. Bone density is decreased in GHD children
2. Growth hormone treatment ensures the recovery of the bone mineral density after the first year of treatment
3. Glucocorticoids and levothyroxine increases the bone metabolism modifications induced by rhGH, at the initiation of the therapy
4. Osteoporosis and osteopenia are most frequently encountered in children with GHD, following multihormonal substitutive therapy

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CONTINUOUS REPLACEMENT THERAPIES IN PEDIATRICS PATIENTS

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Abstract

At the middle of seventies the dialysis equipment starts to improve and new methods arrived in the field of replacement therapies (plasmapheresis, filtration). In recent years, the technique was modified and newer options were made available under the common name of Continuous Renal Replacement Therapies (CRRT).

We want to describe the newest technique for renal replacement and all the advantages and disadvantages for this machinery. We focused the presentation on pediatric CRRT and the advantages of these methods.

Hemofiltration is indicated in the pediatric population for hypervolemia, anuric, in acute renal failure, patients with sepsis, with electrolyte abnormalities, and for catabolic patients with increased nutritional needs, in some poisoning situations.

We need for Romanian children hospitals at least one machinery that can perform CRRT techniques and trained personnel for a performing intervention in emergency.

Key words: Replacement therapies, hemofiltration, children.

Introduction and history of CRRT

Renal replacement therapies applied to critically ill patients have been particularly designed to be simple and easy to be instituted and monitored. This is definitely a contradiction in terms and where the most sophisticated technology might be required for a very delicate task, primitive apparatus and supplies (Ronco et al). In 1977 Peter Kramer, to fulfill the requirement of simplicity, moved from the traditional intermittent hemodialysis to a newly designed treatment named Continuous arteriovenous hemofiltration (CAVH), and then newer options were made available under the common name of Continuous Renal Replacement Therapies (CRRT). The use of a blood pump with a veno-venous blood access became popular (CVVH) and the arterio-venous treatments were partially abandoned. All these modifications are today available as routine treatments.

The basic principles of continuous hemofiltration (HF) are similar for adults and children, but the application of these modalities in children require recognition of the unique properties for pediatric practice. Special attention to aspects such as, extracorporeal blood volume/blood priming (especially in patients < 10 kg), nutritional issues, etiological differences in disease processes (Inborn Errors of Metabolism), access, and line/membrane choice, must be given when dealing with problems in this population.

HF is indicated in the pediatric population for hypervolemic, anuric acute renal failure (ARF), electrolyte abnormalities, catabolic patients with increased nutritional needs, patients with sepsis, poisoning (occasionally in combination with hemodialysis - HD), inborn errors of metabolism, diuretic unresponsive hypervolemia, and hepatic or drug induced coma. Additionally, HF in conjunction with other therapies such as extracorporeal membranous oxygenation (ECMO), and the hepatic support therapies (MARS) has also proven to be quite useful (in Romania - in Iasi and Bucharest two medical teams already use this new method).

Equipment

In the past, blood pumps and fluid balancing systems have been borrowed from the standard hemodialysis technology, while only recently self standing machines have been specifically designed to perform continuous renal replacement therapies.

The simplest machinery often includes a blood pump segment with an air leak detector. What adaptive machinery does not include is the ability to regulate either ultrafiltration control or thermal control. The industry machinery (Gambro, Baxter, B. Braun Medical, Fresenius) offer a variety of warming systems, accurate ultrafiltration controllers, venous and arterial pressure monitor and blood leak detectors. In addition these allow for local prescriptions of HF including continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemofiltration with dialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF (table 1).

Table 1 Available hemofiltration machines.

Company	Machine	Lines
GAMBRO	PRISMA	ADULT+/-PEDS
BAXTER	Accura, etc	ADULT/PEDS
FRESENIUS	2008	ADULT/PEDS
B BRAUN	Diapact	ADULT/PEDS

All systems can provide circuit volumes that offer the adaptability to sustain therapy for smaller and larger size individuals. The Baxter, Braun and the Fresenius machines allow for individual choice of hemofilter membrane while the PRISMA uses a single membrane (AN-69) that has been found in adult ARF data, to improve survival rate.

Vascular access

Standard vascular access utilized for acute dialysis is not adequate to perform high volume hemofiltration. In the majority of the cases, double lumen catheters are providing a large amount of recirculation and an insufficient blood flow. In hemofiltration, while transmembrane ultrafiltration represents the overall amount of fluid removed by the hemofilter, the "net" ultrafiltration represents the real amount of fluid removed from the patient after the re-infusion of the substitution fluid. When high blood flows are required, is recommended to use two separate catheters to permit a reduced resistance of the inflow and outflow, and to reduce the amount of access recirculation. These catheters may be positioned in the jugular and femoral veins without major complications. For pediatric patients the suggested selections for access are figurate in table 2.

Table 2 Size of HF Vascular Access for Pediatric Patients.

PATIENT SIZE	CATHETER SIZE + comp.	SITE / INSERTION
NEONATE	Single-lumen 5 Fr (COOK)	Femoral artery or vein
3-6 Kg	Dual-Lumen 7.0 French (COOK)	Internal/External-Jugular, Subclavian or Femoral vein
	Triple-Lumen 7.0 Fr (MEDCOMP, ARROW)	Internal/External-Jugular, Subclavian or Femoral vein
6-15 Kg	Dual-Lumen 8.0 French (ARROW, KENDALL)	Internal/External-Jugular, Subclavian or Femoral vein
>15-Kg	Dual-Lumen 9.0 French	Internal/External-Jugular, Subclavian or Femoral vein
>30 Kg	Dual-Lumen 10.0 French (ARROW, KENDALL)	Internal/External-Jugular, Subclavian or Femoral vein
	Triple-Lumen 12.5 French	Internal/External-Jugular, Subclavian or Femoral vein

Solutions

The Zimmerman et al studies with adult patients demonstrated that both lactate as well as the bicarbonate based solutions result in the same degree of effective clearance, but plasma lactate levels are higher in patients on lactate-based solutions. Elevated lactate levels may offer mystifying information to the clinician, especially in the setting of sepsis and organ perfusion. Patients with hepatic failure may not be able to convert lactate to bicarbonate, and use of lactate based dialysis solution may produce or exacerbate lactic acidosis, thus bicarbonate buffered dialysis solutions are therefore preferred for patients with hepatic failure. Barenbrock et al demonstrated an improved care of the patient when receiving bicarbonate based solutions when compared to lactate, but the overall data are controversial. Essentially with the use of these products the use of lactate based solutions should be considered historical and potentially detrimental to the child needed CRRT.

Solutions for CVVH can be as uncomplicated as normal saline, lactated ringers, total parenteral nutrition (TPN), routine intravenous fluids or pharmacy made solutions (tables 4 and 5) or other. Many doctors will use saline or lactate of ringers as a relatively inexpensive form of replacement fluid in those patients who are having excessive ultrafiltration. The decision to use replacement fluid is often based on the overall solute and ultrafiltration clearance requirements of the patient as well as the local standard of care. Additionally, pharmacies made customized solutions (usually bicarbonate based) are also available. Some are calcium free dialysate solutions, providing a venue for the provision of either citrate or alternate anticoagulation.

Finally, while it is still controversial whether the substitution fluid should be warmed in standard CVVH, the warming procedure in HVHF is practically mandatory since severe hypothermia may fatally occur when high volumes of fluid are exchanged in a short period of time.

Anticoagulation

If we use high blood flows, anticoagulation becomes less critical since the time of contact between blood and the artificial surfaces is reduced. It should however be remembered that blood viscosity and hematocrit may significantly increase within the filter once high filtration fractions are achieved. In these circumstances, adequate anticoagulation is essential to avoid clots formation. Anticoagulation should be thought about in three different ways. Patients with multi-organ system failure have a natural anticoagulation due to the underlying disease (e.g. sepsis with intravascular coagulation). Those patients may have a natural anticoagulation that may be in the range whereby anticoagulation is not necessary. In those patients obtaining

a high blood flow rate with a large size access may be sufficient to maintain HF without the use of anticoagulation, but is not easy to take the decision. Bleeding secondary to systemic heparinization is always a potential complication.

The majority of studies have shown that heparin is efficient in children. The use of heparin loading at 10-20 units/kg as an initial bolus and then 10-20 units/kg/h maintaining an anticoagulation usually adequate in most patients.

Citrate anticoagulation is performed by adding citrate to the blood as it leaves the patient and returns to the machine. The principle is the same that we usually use in plasmapheresis. The result is an ionized calcium of 0.35 to 0.45 mmol/l within the circuit. Citrate anticoagulation requires a calcium free dialysis bath in order to prevent any potential binding of calcium and any potential risk of coagulation in the HF system.

Citrate also requires a separate central line for calcium replacement

Indications

Prescriptions for acute HF have been for the treatment of acute renal failure (ARF). If one were to suggest a standard prescription, then a blood flow for CVVH would be in the range of 4-6 ml/kg/min trying to keep a venous return pressure of less than 200 mm Hg. Further there is no absolute data to date on the rate of replacement fluid or dialysate fluid. Historically we have used rate of 2000 per 1.73 m^2 /hr for this allows us to compare pediatric data based on body surface area to adult data. Thus in an 11 kilo child who has a 0.5m^2 body surface area, the dialysate or replacement fluid prescribed would be roughly in the 700 ml/hr. The standardization of flow rate as well as ones replacement or dialysate rates allows a better appreciation of steady state drug kinetics, clearance and toxic removal.

Complications of the CRRT

The same complications that occur in other replacement therapies are present in applying hemofiltration. Jenkins et al demonstrated up to a 30% ultrafiltration error rate when using intravenous pumps to regulate ultrafiltration. The only way to avoid the ultrafiltration error is to use industry made equipment that has been purposefully made for ultrafiltration regulation. This will not affect the individual IV pump error rate, but will minimize most of the error seen at bedside.

One of the more biocompatible membranes has been shown to cause a bradykinin release syndrome in patients who are acidotic at the onset of HF or in children who require a "blood prime" in the setting of one of these membranes. These membranes, in the face of interacting with an acidotic plasma environment generate bradykinin which may result in reactions from minor nausea to clinical anaphylaxis.

Children nutrition

For these children it is imperative to understand that HF prescriptions will result in significant amino acid loss across the hemofilter. Data by Davies et al in adults, Maxvold et al in pediatrics and by Zobel et al in neonates has showed that whether one does CVVH or CVVHD, one need to consider the amount of protein calories given to a patient. In non-dialytic setting of ARF the standard recommendation for protein requirements is in the range of 1.5 grams/kilo/day. In patients on HF, in order to maintain adequate nitrogen balance, protein administration may be in the range of 3-4 grams/kg/day. Further in phosphorous deficient dialysate solutions, hypophosphatemia occurs frequently, requiring either a separate phosphorous infusion or additional phosphorous.

Discussion

A retrospective study by Goldstein et al examined outcome in 22 pediatric patients receiving CVVH (D) and controlled for patient severity of illness using the Pediatric Risk of Mortality score. Of the clinical variables studied (glomerular filtration rate, mean airway pressure, patient size or % fluid overload), only the degree of % fluid overload at the time of CRRT initiation differed between survivors (16.4% +/- 13.8%) and non-survivors (34.0% +/- 21.0%, p =0.03), even when controlled for severity of illness by PRISM score using a multiple regression model. This supports earlier data by Fargason et al suggesting that the PRISM score may not be predictive.

A database (Bunchman et al) examined 226 children treated with replacement therapies (HF, HD and PD) looking at predictors of outcome. Diagnosis in these groups varied from ARF to inborn error of metabolism, to intoxications. Similar to adult data, outcome appears to be related not to age, not to modality but to severity of illness and underlying cause of need for RRT. This points out that it is not the modality, but rather the underlying cause of the need for HF, as well as the overall hemodynamic status of the patient (including the presence or absence of vasopressor agents) that affects outcome. Prospective data by the Prospective Pediatric Continuous Renal Replacement Therapy database validates Goldstein's work showing that early intervention with less fluid overload at the time of beginning CRRT improves survival.

In our country in some centers these methods have been were applied, but in few cases, thus no conclusion can be made. In the near future we hope that all the decision making factors can understand that life can be saved with high performance machines and using expensive methods.

The ideal machine should have a small volume, an easy interface and high flexibility (i.e. the ability of performing all types of treatments). The machine must be a self standing equipment, easily transportable at the bedside. Recently, new machines for CRRT have been designed with 4 to 5 pumps. Such machines are not utilized on daily basis, and in some cases the training of the personnel becomes difficult or prolonged. Furthermore, such machines are frequently big, difficult to move and require costly maintenance. The cost of the lines and the entire treatment, including the machine, may significantly increase. In Romania even the commonest machinery performing CRRT is an luxurious one.

Conclusion

Continuous renal replacement therapies appear to be the appropriate treatment in patients with ARF complicated by different clinical problems and other critical situations. In children patients with ARF and other organ system failure, or in patients with a septic syndrome, high volume hemofiltration may be indicated.

For our emergency cases in pediatric units this hemofiltration equipment is mandatory to perform a modern treatment in some desperate situations.

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VON RECKLINGHAUSEN'S DISEASE IN CHILD - A CASE REPORT

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Abstract

Von Recklinhausen Neurofibromatosis is a neuroectodermal dysplasia included in the larger group of phakomatosis; it is an autosomal dominantly transmitted disease with variable penetrance and expression.The authors present the case of a 10 years old female patient with von Recklinghausen disease whose mother has the same pathologic condition. The study estimates somatic development and characteristic clinic manifestations.

Key words: Von Recklinghausen neurofibromatosis, evolution, child.

Introduction

The Recklinghausen disease is included in the family of congenital dysplasia, being characterized by pigmented cutaneous spots (café-au-lait) and benign tumors of the skin, the subcutaneous tissues or perineural (neurofibromes). A positive diagnosis is sustained if more than 6 café-au-lait spots of more than 1.5cm diameter are present. The evolution of the disease is slow; many times patients live a normal life, but often periodical aggravation alternates with stationery ones. Being a hereditary inherited disorder there is no specific treatment for the disease. Continuous follow-up of the patients is important, as possible neurologic complications may appear.

Case presentation

The authors present the patient P.L., female, 10 years old (OD 30791/2004) diagnosed with Neurofibromatosis 1 from the age of 2.

Family history – she has a healthy brother. The mother has the same disease with predominant cutaneous manifestation that appeared gradually after adolescence.

Personal history: the patient is the first born child, from a normal pregnancy, normally delivered at full term; weight at birth – 2400g, height at birth – 48cm, with no neonatal suffering; artificial alimentation from birth; current adequate vaccinations and vitaminizations.

Personal pathologic antecedents: at the age of 8 the patient underwent surgery for excision of a left compressive cervicomediastinal neuroma. For several months she accuses permanent cephalea.

At the moment she presents for clinic and paraclinic re-evaluation.

Physical examination findings:

- severe staturo-ponderal deficit – weight=26kg(below 10th percentile) and height=100cm (below 3rd percentile, -4SD);
- multiple flat, café au lait, round or oval spots, disseminated on the trunk and limbs, having various dimensions, between 0.5 and 10cm diameter;
- left laterocervical cheloid scar after surgical excision of the cervicomediastinal neuroma;
- two soft painless tumors of 0.5 and 1 cm from forehead and the dorsal surface of left foot;
- left palpebral ptosis;
- dorsal cifosis;
- normal mental development.

Paraclinic investigations:

Biological tests: haemoglobin=11,24g%, hematocrit=34%, leukocytes=8500/mm3, segmented neutrophils=63%, eosinophils=4%, lymphocytes=24%, monocytes=6%, thrombocytes=150.000/mm3, ESR (erythrocyte sedimentation rate)=5/9mm, ALT=36U/l, AST=40U/l, urea=23mg%, glycemia=69mg%, seric proteins=6,2mg%, seric calcium= 2,1mmol/l.

Thoracic radiography showed bilateral interstitial reticular and peribronchvascular opacities.

Ventilatory tests- normal values.

Cervical radiography – abnormalities of the C5 vertebra and opacities of the soft tissues at this level.

EEG – rare irritative abnormalities.

Cranial CT-scan found no focal lesions of cerebral substance; the ventricular system was normally positioned, without bone abnormalities.

Slip-lamp examination found iris hyperpigmentation and prominent areas with discoloured border, more numerous in the left eye (Lisch nodules).

Abdominal ultrasonography – normal.

Discussions

Von Recklinghausen Neurofibromatosis is the most common form of the phakomatosis, these being characterised by congenital abnormalities of structures of ectodermal origin like the skin, the nervous system, the retina, and others.

It is inherited as an autosomal dominant trait, but with a highly variable clinical expression among affected individuals within the same family and from one family to another.

A patient meeting two or more of the following criteria can be diagnosed as suffering from Recklinghausen disease:

A. cafe-Au-Lait Spots (6 or more in 100% of cases)

- pre-Puberty: >5 mm greatest diameter
- post-Puberty: >15 mm greatest diameter

B. axillary or inguinal Freckles (2-3 mm diameter);
C. iris Lisch Nodules (2 or more) ;
D. optic Glioma (Optic Nerve benign tumor);
E. neurofibromas of any type (2 or more) or one plexiform neurofibroma;
F. bone abnormalities ;
G. first degree relative with positive diagnosis.

Recommendations are to avoid biopsies.

In our case the positive diagnosis was made based on evident clinic manifestations, including pigmented spots, cutaneous fibromas – which meanwhile increased in number and dimensions; of a great importance was the family positive history – mother presenting a cutaneous form of the disease with gradual evolution without any other suffering. Our patient presents a visceral form, having the compressive mediastinal tumor removed, and also severe development disorders, cervical spine abnormalities, dorsal cifosis, Lisch nodules.

The persistent cephalea led to cranial CT-scan, but no lesions were found.

EEG shows irritative elements but no seizures were present in history, and also the mental development is adequate.

Conclusions

The two related cases of Recklinghausen disease, mother and daughter, confirm the dominant autosomal inheritance, but with onset of the disease at different ages.

Being a genetic disorder a specific treatment is not available, but the follow-up of the patient is important, as neurological complications are possible.

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IV. PEDIATRIC SURGERY

BRIEF REPORT: THE IMPORTANCE OF EP (ENDOTHELIAL CELLS) IN HEMANGIOMAS

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Abstract

Although hemangioma is the most common infancy tumor, its causes remain unknown. Infantile hemangioma is an endothelial tumor that grows rapidly after birth. The initial proliferation of hemangioma is characterized by the clonal expansion of endothelial cells (ECs) and neovascularization. The following article is a literature review on the importance of EPCs (endothelial proliferating cells) in hemangioma development. Being a subject of interest, ECs were investigated in other diseases and medical conditions but, until now, to our knowledge there are few studies that showed direct evidence of EPCs involvement in human vascular tumors.

Key words: hemangioma, endothelial cells, vascular tumors

Introduction

Most hemangiomas are small lesions, but about 10% grow rapidly and because of their size and/or location (fig. 1) they can be problematic and even life threatening.[7]

The life span of infantile hemangioma is generally divided into a proliferating phase (0-1 year), involuting phase (1-5 years), and an involuted phase (5-10 years).[1,2]

Early proliferating hemangioma is composed of densely packed endothelial cells (ECs). These ECs have been described as "angioblastic" and shown to be more embryonic than neonatal microvascular ECs based on morphology and protein expression patterns.[1]

Its pathology is not well known and two theories are postulated at present: on the one hand an intrinsic defect of the precursor endothelial cells that, through somatic mutation in a gene regulating angiogenesis, develop a phenotype that induces clonal proliferation.[3] On the other hand, it might arise from cells originating in the placenta that embolize in foetal tissue during pregnancy or delivery.[3]

The similarities in antigen expression between haemangioma cells and placenta tissue support this second hypothesis.[3]

According to Hamlat et al.[4] the relatively low oxygen environment, in which the human faeto-placental unit develops, during the first trimester, is necessary to induce vasculo-angiogenesis via embryonic endothelial cells proliferation, since these cells are sensitive to hypoxia and acidosis.[4]

In newborn infants with haemangioma, persistent embryonic primitive endothelial cells, trapped in the intimae underneath the developing vessels and representing "leader" endothelial cells, can stabilise the labile vascular endothelial growth factor mRNA (VEGF mRNA) and produce other angiogenic factors, degrade the underlying basement membrane and invade into the stroma of the neighbouring tissue.[4]

The transition from intra- to extra-uterine life is accompanied by more or less pronounced hypoxia. Consequently, in babies with haemangioma, hypoxia can act as a switch to activate these "leader" endothelial cells and thereby initiate a cascade of reactions.[4]

Yu et al.[1] showed that hemangioma-derived ECs are clonal and exhibit abnormal behavior, suggesting hemangioma arises from clonal expansion of a single EC carrying a somatic mutation. Also they hypothesize that endothelial progenitor cells (EPCs) play a crucial role in the hemangiomagenesis, perhaps as precursors of the clonal ECs.

The aim of their study was to determine whether EPCs are present in hemangioma.

EPCs have been found in bone marrow, blood circulation, fetal liver, and skeletal muscle.[1]

Recent studies suggested that EPCs, hematopoietic stem cells (HSCs), and progenitor cells contribute to embryonic tissue vascularization, postnatal organ regeneration, and tumor neoangiogenesis.[1]

Identification of EPCs relies on specific cell-surface proteins. CD133, also called AC133 antigen and human prominin-1, is a novel human stem/progenitor cell marker. Endothelial markers including CD34, CD31, von Willebrand factor (VWF) and the VEGF KDR are expressed by EPCs, vascular wall-derived mature ECs, and subsets of hematopoietic cells, whereas CD133 is expressed only in progenitor cells.[1]

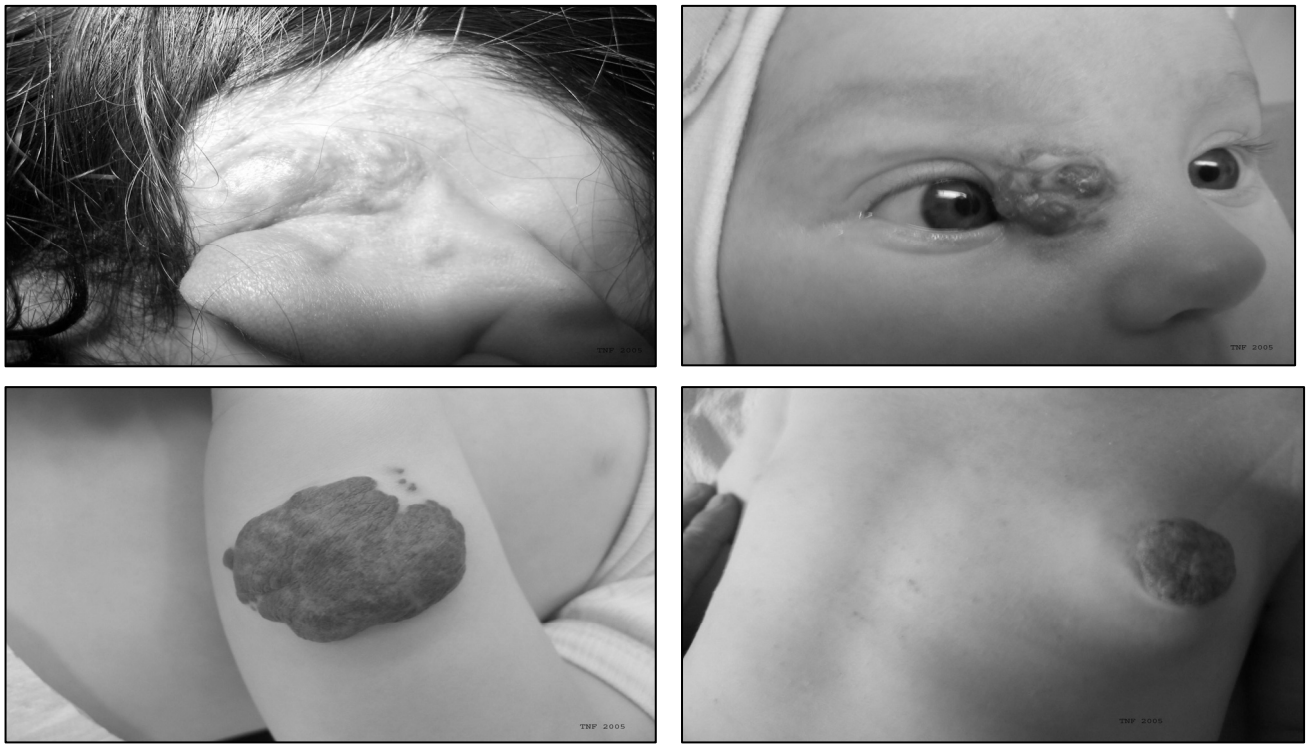

Fig. 1 Hemangiomas located in different parts of the body in 4 patients.

In their study Yu et al.[1] examined CD133 gene expression during hemangioma evolution by Northern blotting and reverse transcription PCR. Using flow cytometry, the investigators showed that proliferating hemangioma contains EPCs that coexpress CD133 and an endothelial marker KDR. These findings suggest that EPCs participate in hemangioma pathogenesis.[1]

In proliferating hemangioma, anti-KDR antibody recognized plump ECs with "immature" morphology, that is large nuclei and scant cytoplasm, lining small nascent vessels but also in the interstitial regions (Fig. 2C). In contrast, flattened KDR^+ ECs were found on the more established vessels in involuting hemangioma (Fig. 2D). The presence of "immature" ECs in proliferating hemangioma is consistent with the CD133 mRNA expression patterns, according to the authors of this study.[1]

Walter et al.[6] suggests that, among EPC in the pathogenesis of the hemangioma a alteration of the VEGF signaling pathway in endothelial and/or pericytic cells could be also to blame.[6]

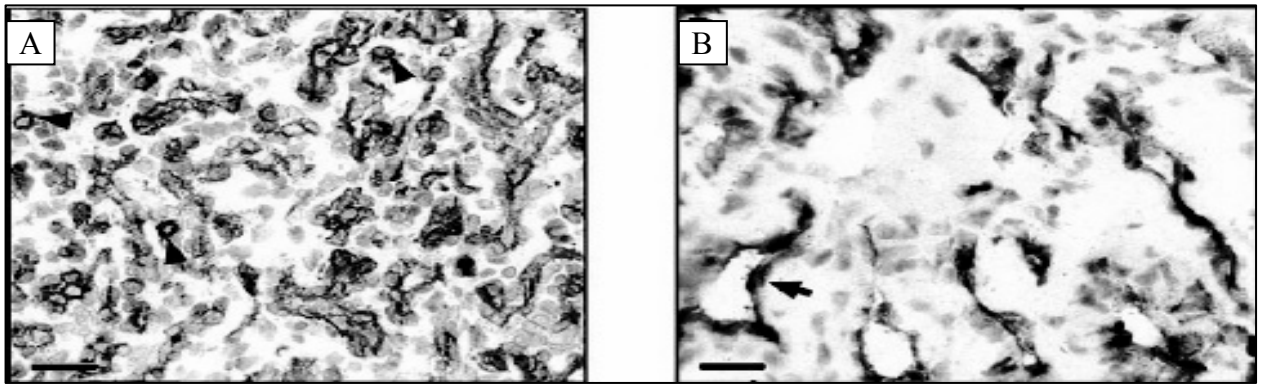

Fig. 2 Endothelial cells evidenced using specific cell-surface proteins: A – intestinal regions, B – involuting hemangioma.

Material and method

The authors of this study investigated the possibility that the tumor is the result of somatic mutation in one or more components of critical vascular growth-regulatory pathways using 15 hemangioma specimens.

Results

Mutations were found in two of the 15 hemangioma specimens: a missense mutation (P1147S) in the kinase domain of the VEGFR2 (FLK1/KDR) gene in one specimen and a missense mutation (P954S) in the kinase insert of the VEGFR3 (FLT4) gene in another specimen. In each case the mutation was detected in tumor tissue but not in adjacent normal tissue.[6]

Identification of EPCs raises the possibility that these cells may give rise to clonal ECs and thereby initiate uncontrolled EC growth. On the other hand we cannot exclude the possibility that EPCs are recruited later from elsewhere during the angiogenesis of proliferating hemangioma.

The question that needs to be answered is if these EPCs, that are involved in hemangioma pathogenesis, originate from bone marrow or a specific tissue.

Boye et al.[7], in an experimental study, showed that endothelial cells from proliferating hemangioma are clonal, and demonstrated that these hemangioma-derived cells differ from normal endothelial cells in their rates of proliferation and migration in vitro.[7] Furthermore, migration of hemangioma endothelial cells is stimulated by the angiogenesis inhibitor endostatin, unlike the inhibition seen with normal endothelial cells.

In an attempt to elucidate the molecular pathogenesis of hemangiomas, the authors tested the intrinsic hypothesis,that the tumors are caused by clonal expansion of vascular ECs. They isolated ECs from proliferating hemangioma in nine infants and the multifocal hemangioendothelioma lesions in one infant.

After that the investigators assayed cell samples from eight of the ten patients for monoclonality and found them all to be clonal, further demonstrating that hemangioma-derived ECs differ from normal ECs in rate of proliferation and migration in vitro, as well as in their response to an angiogenesis inhibitor endostatin.

These results indicate that hemangiomas do indeed constitute clonal expansions of abnormal ECs. The findings are consistent with the possibility that hemangiomas are caused by somatic mutation(s) in a gene(s) that regulates EC proliferation.

Boye et al. [7] concluded that hemangiomas constitute clonal expansions of endothelial cells.

Conclusions

We believe that the data provide support for the hypothesis that hemangiomas are caused by an intrinsic abnormality of ECs. However, it is possible, that all hemangiomas are not due to the same underlying defect. Thus, in some cases, the primary defect could exist external to the proliferating ECs.

It is also possible that even in hemangiomas caused by somatic mutations in ECs, different genes may be involved in different patients. Elucidation of the mutated genes in each case will enhance our understanding of the molecular control of EC proliferation, and the potential for antiangiogenic treatment of hemangiomas.

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ESOPHAGEAL ATRESIA AND TRACHEESOPHAGEAL MALFORMATIONS

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Abstract

Tracheesophageal fistula (TEF) and esophageal atresia (EA) are surgical emergency, presenting during first moments after birth. They are usually associated with other congenital anomalies. They are usually complicated due to aspiration of gastric contents leading to pneumonia and respiratory distress. The anatomy end embryology of the esophagus, clinical manifestations, diagnosis and management of these conditions are presented in this paper work.

Key words: tracheesophageal fistula, esophageal atresia.

ANATOMY OF ESOPHAGUS

Layman calls it *food pipe*, an organ responsible for delivering food to stomach. It is a tabular structure with diameter of 2.5 cm and length 25 cm. Hence, it is important to note that whenever we want to instrumentise esophagus e.g. for nasogastric feeding or decompression, that its upper end lies at distance of 15 cm from incisors and lower end of esophagus lies at 40 cm.

Like rest of gut, esophagus also has the capacity to do peristalsis. Peristalsis is actually responsible for delivering food bolus to stomach.

According to the region, esophagus traverse is divided into:

- cervical esophagus
- thoracic esophagus
- abdominal esophagus

- Cervical esophagus starts from lower end of oropharynx, at the level of C_6.
- Thoracic esophagus lies in the mediastinum. At the level of T10, thoracic esophagus crosses diaphragm, a strong muscular layer separating thorax and abdomen.
- Abdominal esophagus at the level of T_{11} enters into stomach, forming a very sharp angle called cardiac angle.

Arterial supply of esophagus

It is very important to know the blood supply of esophagus, when we want to operate on esophagus. It has got complex blood supply according to anatomical division of esophagus from various arteries:

- *cervical esophagus:* Receives its blood supply from inferior thyroid artery
- *thoracic esophagus:* Receives its blood supply from branches of thoracic aorta and branchial artery
- *abdominal esophagus:* Receives its blood supply from left gastric artery and left inferior phrenic br. of abdominal aorta

Venous drainage of esophagus

Like arteries different veins drain esophagus:

- *cervical esophagus*: drained by inferior thyroid vein
- *thoracic esophagus*: drained by azygous vein, hemiazygous vein and accessory hemiazygous vein
- *abdominal esophagus*: drained by azygous vein and left gastric vein

Lymphatics of esophagus

- *cervical esophagus*: drained into deep cervical and paratracheal nodes
- *thoracic esophagus*: drained into mediastinal nodes
- *abdominal esophagus*: drained into nodes in relation with left gastric artery

Nervous supply of esophagus

Esophagus is supplied by autonomic nervous system both sympathetic and parasympathetic nerves.

- sympathetic nerves reaches it through splanchnic branches of sympathetic trunk
- parasympathetic nerves reaches it through vagus plexus around it.

EMBRYOLOGY OF ESOPHAGUS

Human fetus has been divided into *foregut*, *midgut* and *hindgut*. Esophagus develops from the part of foregut between pharynx and stomach. In early stages of development, it is short but elongates as formation of neck, descent of diaphragm and with enlargement of pleural cavities.

The muscles of esophagus arise from *mesenchyme* surrounding the foregut. Upper two third of esophagus is made up of striated muscles and lower one third is made up of smooth muscles.

Whole respiratory system develops from *median diverticulum* of foregut. That's why, its lining epithelium is derived from *endoderm* and connective tissue, cartilage and muscles are derived from *mesoderm*.

Free caudal end of diverticulum becomes *bifid*, each subdivision being called *lung bud*. Part of diverticulum cranial to this lung bud forms *larynx and trachea*, while lung buds form *bronchi and lungs*.

About 19th day of gestation, the foregut of human embryo is represented by a cell-layer tube, which extends from pharynx to stomach. Over several days, the ventral aspect of this foregut begins to thicken and form a groove lined by ciliated, stratified, columnar epithelium which becomes *respiratory mucosa*.

Separation of the dorsal foregut (esophagus) from tracheal ventral part occurs first at the carina and extends in a cephalad direction. By about 26th day of gestation, these two structures become up to level of larynx. Bronchi develop from posterolateral buds of trachea and grow to each side. This process of separation of dorsal and ventral foregut is called *epithelial 'ridge' ingrowth*.

HISTORY OF DISEASE

Thomas Gibson was the first, who in 1696 described an accurate clinical and pathological description of the most common anomaly, in which EA is associated with TEF. At that time this disease was considered as fatal condition, which is the not fatal anymore now days. Major breakthrough occurred in 1941, when American surgeon *Cameron Haight* achieved survival by successful anastomosing two ends of esophagus and thus overcoming obstruction in gastro-intestinal tract.

DEFINITIONS

Atresia: Means absence of a normal opening in hollow tract.

Fistula: Means an abnormal connection between two epitheliased structures in body.

Esophageal Atresia: This is a congenital disorder, when proximal and distal portions of Esophagus do not communicate. The proximal blind pouch has thick musculature and bigger diameter, while the distal portions have thin musculature. The proximal pouch usually lies at the level of T_2-T_4, but can be as short as up to C_7 and longer up to T_5.

Tracheesophageal Fistula: This is also a congenital disorder with abnormal disconnection between anterior esophagus to posterior membranous trachea. Occasionally, trachea trifurcates with fistula arising between two primary bronchi. Rarely, fistula connects with bronchi.

CLASSIFICATION

These 2 abnormalities are congenital, that means they are present before birth. They can occur as separate entities but commonly occur together.
(see fig. 1)

- *EA with distal TEF (84%)*: This is most common type of deformity among all. Here, a gap exists between two Esophageal segments. The length of this gap actually influences the simplicity and difficulty in correction. Occasionally, an overlap of segments and even muscular continuity exists. (fig. 1A)
- *EA with proximal fistula (1%)*: This is a least common type among all. Here fistula usually arises at 1-4 cm proximal to the tip of upper esophageal pouch. (fig. 1B)
- *EA with proximal and distal fistula (3%):* Here in this abnormality there is usually no gap exists between two segments of Esophagus. So very easy to repair. (fig. 1C)
  - *Type 3A EA with proximal and distal TEF with gap of >2cm*
  - *Type 3B EA with proximal and distal TEF with gap of <2cm*
- *Isolated EA (without TEF) (8%)*: Here in this abnormality usually a long gap exists between two segments of Esophagus. Stomach is small because no amniotic fluid reaches the stomach in uterus. (fig. 1D)
- *Isolated TEF (no EA) (4%)*: Fistula is usually 2-4 mm in diameter occurs at any level from Cricoid to Carina but usually arises in lower cervical or upper thoracic area. Double or triple fistula can also occur. "N" type or "H" type indicates integrity of Esophagus. (fig. 1E)
- *Repaired esophageal atresia with distal TEF*: (fig. 1F)

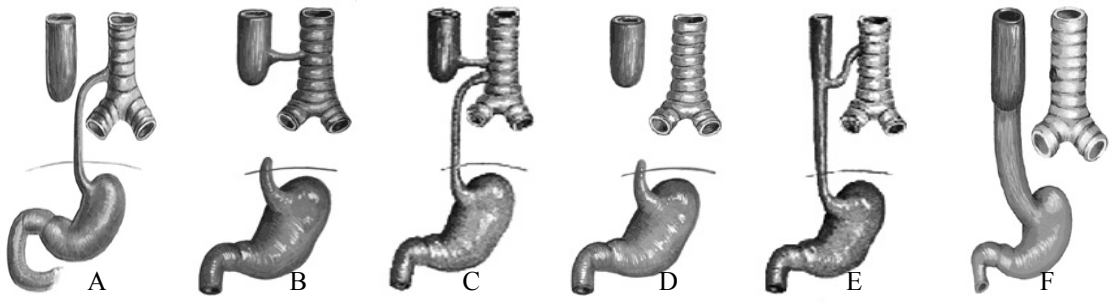

Fig. 1: Esophageal Atresia: A. with a distal tracheo-esophageal fistula, B. with a proximal fistula, C. with fistulae from both esophageal segments, D. isolated esophageal atresia without a fistula, E. TEF of the 'N' or 'H' type, F. repaired esophageal atresia.

Esophagus of all affected infants is deficient in neural tissue in *Auerbach's plexus*. Lower segment is more deficient than upper segment. This is the cause of a*bnormal peristalsis* demonstrated by Barium Swallow. *Manometric studies* have showed that this defect is congenital not result of operation. Discoordinated peristalses have been reported from level of fistula to the stomach in patient with isolated TEF.

ETIOLOGIC FACTORS AND PATHOGENESIS

Even today etiologies of all these congenital anomalies are not known completely but many theories have been postulated by different embryologists. But for parents of children with this anomaly, it is important to understand – it is not their fault and they could not have done anything to prevent it.

This defect may be result of interruption of process called *epithelial 'ridge' ingrowth*.

Smith's Theory of EA: This is the most widely accepted theory for formation of EA. He postulated that 'Lateral Esophageal Grooves' (naturally occurring areas of narrowing much like the ridges of epithelial proliferation that form the septum between Trachea and Esophagus) may turn dorsally and in formation of EA

There exists no convincing evidence of Mendelian Inheritance, however number of reports of multiple family members having EA and TEF exist. Several sets of identical twins having EA and TEF have occurred as well as mother and child and father and child have occurred.

The non random association of VACTERL may be evidence of generalized disturbance in embryogenesis. The exact nature of embryogenic insult that cause EA/TEF is not known but there is some evidence that vascular insufficiency; genetic factors; vitamins deficiency drug and alcohol exposure and viral, chemical and physical external events results EA/TEF.

EPIDEMIOLOGY

a. *Frequency*: 1 in 4000 live births has EA/TEF. Also incidence increases in 1st degree relatives.

b. *Race*: There is no association with any specific race, but in general white population have increased risk of having EA/TEF than non white population

c. *Sex*: Male to female ratio is 1,26.

d. *Age*: Recent studies have shown that EA/TEF increase in incidence with increase in maternal age (> 30 years)

PATHOPHYSIOLOGY

Normally Trachea and Esophagus are entirely separate lumen with no connection in between them. Hence, child can feed properly without any respiratory distress and feeding problems.

- But in case of isolated EA, there is accumulation of saliva and food in proximal pouch. Thus there is increased risk of aspiration of these collections resulting respiratory distress, atelectasis and pneumonia.
- When proximal pouch is associated with Proximal TEF, result definitely into an aspiration of various collections of proximal pouch result into various morbid conditions.
- EA with distal TEF is more fatal condition because this allows two way movements of gastric fluids and gases.
- When there is H/N type or isolated TEF, symptoms are less severe because some of Gases and Fluids went via esophagus to mouth.
- Also because of congenital deficiency of neural tissue in Auerbach's plexus there is in coordination in peristalsis in esophagus of infants with EA/TEF. These are demonstrated by manometric and gastrostomy. They even persist after surgical repair of defect.
- Tracheal and pulmonary development have been hampered in fetus with EA/TEF because:
  - Swallowing of Amniotic Fluid results Dilation of Proximal Esophageal Pouch, this cause increased pressure on Trachea. These results into mal development of cartilage rings called *Tracheomalacia*.
  - Also TEF causes flow of Pulmonary Amniotic Fluid to pass into stomach, this results in decreased branching of Bronchi and Alveoli because of decreased Intra Pulmonary pressure.

CLINICAL PRESENTATION

- excessive salivation
- drooling
- poor feeding
- coughing, choking and gagging associated with attempted feedings
- bluish coloration of skin associated with attempted feeding.
- excessive amniotic fluid during pregnancy (polyhydroamnios)

The first sign of EA in fetus is Maternal Polyhydroamnios which has got broad differential diagnosis:

1. agnathia, microstomia, synotia
2. DiGeorge velocardiofacial syndrome
3. placental insufficiency
4. maternal dm
5. chromosomal disorders, iso-immunologic diseases, congenital abnormality
6. epignathus
7. hydrolethalus
8. tetra logy of fallot, treacher collins syndrome
9. myasthenia gravis, pseudohypoaldosteronism

Also polyhydroamnios is associated with *premature birth* because of increased amniotic pressure. About one-third of infants with EA weigh less than 2500 gm. If there is associated TEF then there is decrease in amniotic fluid amount.

Classically, the neonate with EA presents with copious, fine, white frothy bubble in mouth and sometimes in nose. These secretions may clear with aggressive suction but return. There are episodes of cough, choking and cyanosis, typically exaggerated with attempted feeding.

Cyanosis is a result of laryngospasm (a protective mechanism that body has to prevent aspiration into trachea). Over the time respiratory distress develops.

Abdomen is distended if there is associated TEF and scaphoid if there is isolated EA

Hence, in newborn prematurity, polyhydroamnios and any demonstrable element of VACTERL warrants a more thorough search for EA.

DIAGNOSIS

EA with or without TEF, is a fairly common congenital disorder of a neonate who develops feeding difficulties and respiratory distress in the first few days of life. Early diagnosis is necessary to minimize pulmonary complications.

A. Prenatal diagnosis

- *Prenatal maternal sonography*: Although sonography postnatally has no significance in evaluation of EA with/without TEF, but prenatal maternal sonography is suggestive of these possible conditions.
  - *Pouch sign*: This is usually seen as aechoic shadow in middle of fetus during 26th week of gestation. This is confirmatory for EA. But this requires experience.

- *Presence or absence of gastric air bubble* suggests EA with TEF or isolated EA respectively.
- *Polyhydroamnios* is also present.

The prenatal diagnosis of EA is low, unless there is *pouch sign* and *polyhydroamnios* together.

Polyhydroamnios alone is a poor indicator of EA. Only 1 out of 12 patients with polyhydroamnios has EA. Similarly, a small or absent fetal stomach gas bubble has multiple association in addition to EA. Prenatal sonography can also cause many cases of TEF to be missed because amniotic fluid from lungs may pass to stomach and result is normal appearing fluid filled stomach shadow.

- *Prenatal MRI of fetus*: Today in the time of modern diagnostic tools, MRI is important confirmatory diagnostic of EA/TEF prenatal. This allows visualization of entire lesion and anatomic relationships unlike sonography. In modern medicine this is a method of choice. This also allows recognition of other associated congenital anomalies. However fetal MRI is difficult in polyhydroamnios because of poor image quality, also fetal movements cause poor imaging.

This is 100% confirmatory. However doubtful cases should be screened for EA/TEF postnatal.

B. Postnatal diagnosis

- *Nasogastric Intubation of Neonate*: Here we prefer to use 8F in premature and 10-12F intern infants. We perform this technique when we suspect EA either by prenatal sonography or by clinical picture of neonate.

Normally gastric cardia of infant's lies at 17 cm from gums of infant, but in case of EA, tube typically stops at 10-12 cm. This technique is not confirmatory as external compression of esophagus can lead to false positive test. In this case repeat the test. If we are using soft tube, then it may coil inside the pouch and can lead to false negative test. Hence, nasogastric intubation should always be followed by whole chest and abdomen simple radiography.

This is very low for this technique as lots of false positive and false negative test results associated. Also tear of oropharynx or esophagus should be considered especially in patient, who underwent various attempts at feeding tube placement following delivery. Also with this technique we can not differentiate between types of EA/TEF.

- *Radiography*: This is very important diagnostic tool and should always follow nasogastric intubation. Here both PA and lateral views should be taken. Both chest and abdomen should be included in single radiograph for correct diagnosis of EA/TEF with type. With this we can also confirm location of aortic arch, which is important regarding surgical repair of defect. Also we can detect congenital anomalies like cardiac silhouette: boot shape cardiac shadow in tetralogy of Fallot, vertebral anomalies, aspiration pneumonia especially of right upper lobe and patchy atelectasis are frequently present. Localization of aortic arch is important because thoracotomy is always done on the side opposite to aortic arch.

Radiographic signs of right sided aortic arch

A. Right ascending Aorta, indicated by an opaque shadow on right side of mediastinum.
B. Right sided tracheal indentation and/or deviation.

We can also know the position of aorta be passing umbilical artery catheter, by seeing on which side of vertebral column its shadow lays.

Although barium studies are rarely indicated because of high risk of aspiration chemical tracheobronchitis but sometimes to measure the length of gap between proximal and distal esophageal pouch. Here we put contrast material in proximal pouch through mouth and in distal pouch via gastrostomy, and measure length of gap and also helps in visualizing other gastrointestinal abnormalities.

Radiographic findings on children with EA/TEF according to type of anomaly present

a) *Isolated EA*
- Dilated air filled blind Proximal Pouch, which often displaces trachea anteriorly
- A gasless abdomen may be depicted. Air is normally present in stomach even after 15 min of birth
- Lower pouch can be seen by gapogram or air

b) *EA with TEF Distal*
- Proximal pouch and gaseous stomach and small bowel (because air passes through fistula)
- Images may be airless if TEF is occluded
- Excessive air may be present in esophagus, although some air in esophagus is

normal in neonates and children because of aerophagy common in bottle fed infants

c) *EA with TEF Proximal*

- Similar to isolated EA on plain X-Ray
- Barium swallow examination may fail to demonstrate this anomaly
- Fistula visualization requires rapid sequence or videoflouroscopic studies during cautious filling of proximal pouch

d) *Isolated TEF*

- Recurrent pneumonia may be present with a widespread pneumonia pattern
- Fistula delineation is difficult
- Excessive air may be present in esophagus

If H-Fistula is strongly suspected on clinical basis, a prone video-esophagogram should be obtained to determine fistula's size and location.

Stringer technique: Patient lying prone on waist height footstep with fluoroscopic table erect and by using cross table flouroscopy, serial injection of isotonic, non ionic contrast agent or dilute barium is administered through a naso-esophageal catheter. As the catheter is withdrawn proximally, tracheal filling is noted at situ of fistula.

Finding of a coiled nasogastric tube at radiographic examination confirms EA. Occasionally; the tube may coil because of external esophageal compression and here repeat placement should be attempted. If the tube passes to stomach, the possibility of the tube passing through a TEF must be investigated. The infant's cry should be profoundly affected if the tube passes through vocal cords on the way through a distal TEF and into stomach.

Special Concerns in Contrast Radiography

A. Contrast radiography has no special role in diagnosis of EA/TEF, except for localizing TEF.

B. Barium is best contrast material but can cause aspiration pneumonitis and pulmonary edema.

C. Extra luminal barium causes granulomatous and fibrotic reaction. Hence fibrous mediastinum.

D. Aqueous low osmolality agents such as Visipaque and Optiray are preferred. They are expensive but have no deleterious effect on gastro intestinal tract. It is preferred in premature children and neonates with suspected esophageal perforation. They also remain in gastro intestinal tract for long time because of low absorbability (because they are hyperosmolar and hypertonic)

E. Hypo-osmolarity aqueous agents get quickly diluted and are less fluoroscopically visible because of they have low coating ability.

F. They also cause hypovolemia, severe dehydration and pneumonitis by significant irritation of trachea and bronchi.

G. Hence, contrast radiography of neonates with EA/TEF should be done under experienced hands.

- *Tracheoscopy and esophagoscopy*

They have no diagnostic value but can be used to confirm the position of TEF.

DIFFERENTIAL DIAGNOSIS

- Esophageal cancer
- Esophageal diverticula
- Esophageal rupture
- Esophageal stricture
- Esophagitis
- Gastresophageal reflux disease
- Pneumonia, aspiration
- Respiratory failure
- Tracheal tumors
- Tracheomalacia
- Zenker diverticulum

ASSOCIATED ANOMALIES

- Congenital heart diseases, intestinal atresia, imperforate anus, skeletal anomalies and renal anomalies suggest VACTERL association: **v**ertebral, **a**nal, **c**ardiac, **t**racheal, **e**sophagus, **r**enal, **l**imb
- Esophageal Atresia may also be seen in the CHARGE association: **c**oloboma, congenital **h**eart disease, choanal **a**tresia, growth and mental **r**etardaion, **g**enital hypoplasia, **e**ar anomalies

Approximately half of the patients with EA with or without TEF have associated anomalies. Many of these are major and adversely affect the patient's immediate and long term outlook. Associated anomalies, in fact, cause substantially more deaths than malformations. Smaller birth weight infants have more anomalies than the larger birth weight one. Associated anomalies are found 3 times more often in infants weighing less than 2000 gm than those weighing 2500 gm. Isolated EA have more incidence of associated anomalies with any type of anomalies. Infants with VACTERL association tend to have a higher proximal esophageal pouch and more complications with higher rate of mortality. VACTERL association is not a syndrome but a non-random association. If an infant has one of these anomalies another one should be suspected.

Cardiac anomalies are most common and most lethal. Gastrointestinal anomalies are frequently seen but correctable. A variety of anomalies both trivial and serious occur. Some are more immediate risk to life and require treatment before EA and TEF repair. The majority of the anomalies, however, do not interfere with immediate care of infant.

MANAGEMENT

I. Pre-operative management

- confirming the diagnosis and type of anomaly
- evaluating the pulmonary status, treating the pulmonary problem and preventing tracheal contamination
- searching for and if necessary treating other major associated problems

Diagnostic procedures described earlier should be done as soon as after initial assessment and support is provided.

Pulmonary status is evaluated by respiratory rate, degree of respiratory distress, cyanosis, rales or rhonchi and chest radiograph. Occasionally, oxygen saturation and blood gases valve is obtained. To present further aspiration, pharynx should be suctioned continuously. Patient should always be cared in Fowler's position, with head elevated at approx 45^0. This position helps in minimizing the amount of gastric fluid that refluxes back through the distal TEF into trachea by placing the gastresophageal junction above the level of gastric fluid, so that regurgitation is more likely to evacuate gas than liquid. All the patients should be put on combination of Ampicillin and Gentamicin, to cover broad spectrum. If there is clinical or radiographic evidence of significant atelectasis or pneumonia, a decompression Stamm gastrostomy should be done, in order to prevent further gastric reflux through distal TEF and its consequences. Significant improvement of atelectasis or pneumonia prior to major thoracic procedure results in smoother operative and postoperative course. Patients usually respond well within 24 to 72 hrs, at which time the anomaly is repaired.

As we all know major cause of death in these pediatric patients is concomitant disease, so systematic evaluation is of great value. Some conditions need specific therapy and responds well to therapy are congenital heart disease, idiopathic respiratory distress syndrome (IRDS), intestinal and anal atresia etc.

IRDS is a difficult problem to manage. Infants having this require mechanical ventilatory assistance, often with significantly increased intratracheal pressure. Presence of TEF results distension of stomach and further respiratory distress because of diaphragm elevation. This stomach distension frequently leads to gastric rupture, if not vented by gastrostomy. Gastrostomy causes decompression of trachea via fistula to a degree that sufficient intratracheal pressure can't be maintained to provide adequate ventilatory support. This problem can be overcome by temporary occlusion of TEF with Fogarty balloon passed bronchoscopically. A more permanent and secure occlusion is division and suture of TEF as an urgent procedure.

Laryngotracheoesophageal cleft or congenital subglottic stenosis associated with EA or TEF usually requires a prompt tracheostomy.

Some premature infants, those who are quite ill when the cause is not readily apparent, and those who are septic, benefit from a period of support, evaluation and therapy prior to esophageal repair. These patients plus those with major anomalies are probably best treated by gastrostomy to prevent gastresophageal reflux and its consequences, by central venous catheter for parenteral nutrition and by antibiotics and other appropriate therapy – surgical or medical. When patient stabilizes and begins to improve, EA/TEF repair should be done. Timing is obviously important.

II. Operative management

Repair is performed under general anesthesia. During repair of EA/TEF needs serious involvement of anaesthesiologist in surgical field also, other than anesthetic management. It is he who guides the surgeon in locating and identifying fistula and proximal end of esophagus.

After making a posterolateral incision just below the tip of the scapula, the latissimus dorsi and the serratus anterior muscles are retracted anteriorly. The fourth rib is resected subperiosteally, an incision is made through the deep periosteum. The cut edges are grasped with small mosquito clamps. The plane of endothoracic fascia is developed with blunt dissection. The pleura are gently dissected from chest wall posteriorly to the apex of the chest and two to three interspaces below the incision. If a small opening is made in the pleura, it is closed with small ligature.

The dissection follows the curve of the ribs to the mediastinum. The azygos vein is retracted anteriorly with pleura after dividing the two highest intercoastal veins, as they enter the azygos. The vagus nerve is identified, as it runs along the right side of both the proximal and distal esophagus.

The distal esophagus is identified, looped and freed up to its junction with the post trachea. Traction sutures are placed on the tracheal end of the fistula, which is divided close to the trachea. The trachea must not be narrowed. The tracheal end of the fistula is closed with interrupted sutures. Adjacent tissue, if available is tacked over the closure.

Traction sutures are placed in the end of the upper pouch. The proximal esophagus is freed well into the neck. A proximal pouch fistula to the trachea is possible. The dissection stays close to the pouch. The vagus nerves are avoided. The distal esophagus is freed only as much as necessary to approximate the ends of the Esophagus.

The end of the upper pouch is excised. The posterior row of sutures are placed through all layers of the esophagus and tied inside the lumen. The anterior row is tied on the outside. A 10F catheter is left in the reteropleural space near the anastomosis. The wound is closed in anatomic layers.

Summary of management

- Feeding is withheld and suction applied to esophageal pouch
- Nursed in head elevated position
- Associated congenital abnormalities are identified
- Surgery required with in first 24 hrs of life
- Operation involves
  1. right thoracotomy and extrapleural approach
  2. azygos vein is divided
  3. TEF is divided
  4. esophagus mobilized and primary anastomosis is usually achieved
  5. if anastomosis impossible, a staged procedure is required
  6. gastrostomy performed and fistula divided at initial operation

7. esophagus replaced by colon or stomach after a few months

Situation

For infants with long gap EA, however, the operation may be much more difficult and the results not always good. The two ends of the esophagus may be thought to be too far apart, or the tissues too thin, raising concern that the repair would be under too much tension and not hold up. Whether the gap is merely long or too long depends on these factors and the viewpoint of the surgeon. For gaps 2-3 cm long or 2-4 vertebral bodies apart, a primary repair will usually be carried out. Surgeons are realizing that some tension will be tolerated by a well constructed anastomosis. As the distance increases, however, so do the likelihood of complications with an attempted primary repair. To avoid this possibility, many surgeons will use an esophageal substitute such as stomach or colon.

a. The True Primary Repair

Despite the difficulties imposed when a long gap is present, we believe a true primary repair using the child's own esophagus will be best for the long term. A true primary repair can be defined simply as joining the two esophageal ends together and leaving the stomach entirely below the diaphragm. The stomach must remain in the abdomen where it belongs. Furthermore, no circular incision is made through the esophageal muscles. A circular cut through the muscle wall will allow the remaining tissue to stretch; a circular myotomy. Circular myotomies are not used because of the potential for complications from the weakened esophageal wall. The area of myotomy is unsupported by muscle and may balloon up to a serious degree.

With the esophageal ends joined together and the stomach below the diaphragm, the child has by far the best chance of eating normally. Later problems are also much less likely to occur.

The result of a true primary repair is always the same, the esophageal ends are joined together and the stomach kept below the diaphragm. For most of these infants it can be done at one operation. This has proven true, even if there is a long gap between the esophageal ends. The two esophageal ends can be brought together, even sometimes under a great deal of tension and the repair will still hold together. Therefore, even babies whose gaps are rather long can have an initial true primary repair.

b. Stimulating the esophagus to grow

It is not always possible, however, to do a true primary repair initially. If the child has been born with most of the esophagus missing or the first operation has failed, or the upper pouch has been brought out the neck (a spit fistula), the gap will be too great for an immediate (one step) true primary repair. For these children, the esophagus must be made to quickly grow so the repair can be accomplished. We have found that the growth will be rapid and may take only a few days or, at most, 12-14 days. Over this relatively short period of time, the ends of the esophagus will grow significantly and allow a true primary repair to be carried out. The rapid growth of the esophagus is the most important discovery we have made and allows these operations to be carried out.

At the first operation, the two esophageal ends are put on traction towards each other. Occasional, when the gap is not overly long, the traction sutures will rapidly stimulate enough esophageal growth relatively rapidly. When this appears to be the case, the traction sutures are placed internally. After 2-3 days time, the incision is reopened and the esophageal ends sewn together.

For the very longest gap infants, however, more time will be needed. The traction sutures are placed in the esophageal ends and brought through the skin to the outside of the chest wall. This allows the traction to be increased daily and maximizes the growth stimulus. These children are kept on the ventilator and heavily sedated so they do not tear the traction sutures loose. Even the very longest gaps rapidly respond to this growth stimulus. When the ends are virtually together, the infant is returned to the operating room and the esophagus joined.

c. Esophageal Substitutions (Interposition Grafts)

Usually at other hospitals, if the gap is very long a true primary repair is not recommended or attempted. If the esophageal ends can not be brought together then another tubular organ must be used to bridge the gap and provide continuity. The most commonly used esophageal substitutions; include colon interpositions, the creation of a stomach tube or a pull-up of the stomach (gastric transposition).

The interposition grafts, with the exception of the jejunum, cause increasing problems and severe consequences with time. Pulling part of the stomach up into the chest so that the two esophageal ends can be joined together is not a true primary repair. Any partial division or elongation or an upward pull-up of the stomach will lead to significant long term consequences and would not meet the definition of a true primary repair.

The most commonly used esophageal substitutions include colon interpositions, the creation of a stomach tube or a pull-up of the stomach (gastric transposition). The consequences of these will be discussed under early and long-term results but suffice it to say, the likelihood of a difficult early course is high.

III. Post-operative management

The intubated patient is transported to neonatal intensive care unit. Antibiotics are continued until the chest drain is removed and endotracheal tube is suctioned necessary. Oral suctioning to a depth of no more than 7 cm from the lips is performed every half an hour on the first day, then every hour or more frequently as necessary on second day. The chest draining tube is placed in 2 cm of water, only to seal it (under water seal), it is not connected to a suction pump as this encourage an anastomotic leak. Morphine is infused as necessary for patient's pain relief and peripheral parenteral nutrition should be commenced. Endotracheal tube should remain in place to ensure ventilation. Premature extubation and subsequent

reintubation in the setting of a freshly closed tracheal fistula invites reopening of the fistula.

Watch for saliva exiting out the chest drain, this is a signal of anastomotic leakage. Often, it is accompanied by visible distress. Signs of sepsis may or may not be present. A chest radiograph should be obtained. Provided that the baby is stable, a contrast enhanced study of the esophagus with soluble isotonic medium may be performed on day 6 or 7 to assess for leaks and to view the repair. If the esophagus is patent and reasonably sized, the baby may be feed starting with expressed breast milk is ideal. Then the chest drain is removed. As soon as the baby feeding well, the intravenous line is discontinued and the baby can be discharged. Oral ranitidine prescribed for 6 months because of propensity for gastresophageal reflux in this group of patients and because of the risk of strictures as a secondary effect.

FOLLOW-UP CARE

If all is well with the patient and if the parents have been briefed on what to look for, reasonable follow up regimen may include the following steps:

- Make contact with the community physician who is responsible for general medical condition of child and ensure that he or she is briefed on the baby's history, condition and expected outcome
- The nurse in the surgical team should follow up by telephone in one week
- The surgeon should follow up in one month to interview the parents and generally assess the condition, growth and heavily at the surgical site
- The patient should return at 3 months for a similar assessment
- At a 1-year follow up and general assessment, a swallowing function, respiratory issues and gastresophageal reflux should be addressed

Radiologic assessment of the esophagus is required only if a significant history of choking, cyanosis, regurgitation, dysphagia, growth failure, coughing or wheezing exists. Subsequent endoscopic evaluation can be performed as indicated.

Follow-up care when the child is older can be performed as needed. Specific reassessment of patient which is aged approx. 12 yrs is advised; at that time, endoscopic assessment of the patient should be planned. Barrett esophagus and even subsequent malignant change is possible in condition because of the propensity for gastresophageal reflux. Follow-up with periodic endoscopy every few years until the patient is an adult can be justified for this reason.

PROGNOSIS AND COMPLICATIONS

The majority of patients will experience few problems after initial period. However, for others, problems may persist for many years:

- swallowing problems
- stricture
- gastresophageal Reflux
- long gap esophageal atresia
- tube feeding
- respiratory problems

Traditionally, the prognosis for children with EA/TEF was centered on the Waterston Risk Classification, which is based on the birth weight and presence of pneumonia and associated congenital abnormalities. Because of advancements in Neonatal Care, however, this risk classification is no longer prognostic. Pneumonia may be successfully treated, except in some infants with severely low birth weight. Currently, cardiac and chromosomal abnormalities are the most significant causes of death. Regardless of classification scheme, infants with a birth weight less than 1500 gm, major cardiac abnormalities, severe associated anomalies, preoperative ventilator dependence, and/or a long gap are at increased risk.

Preoperatively, the greatest risk to the child with EA/TEF is aspiration gastric rupture has been reported in patients with TEF who are receiving ventilator support. Air is forced through the fistula into the distal esophagus and then into the stomach.

The severity of complications after EA/TEF repair is often dictated by the extent of repair required. Primary anastomosis and fistula closure has fewer complications than esophageal replacement. The most common complications include anastomotic leakage, recurrent fistula, stricture and gastresophageal reflux.

Anastomotic leakage into mediastinum occurs in 14-21% of children that have undergone a surgical repair of EA/TEF. Leaks usually results from small friable lower segment, ischemia of esophageal ends, excess anastomotic tension, sepsis, technically poor suturing techniques and inaccurate mucosal apposition. Most leaks are small, occur later (after first 48 hrs of repair) and require only conservative management with cessation of oral intake. Total Parenteral Nutrition (TPN) and antibiotics are needed. Spontaneous healing occurs in 95% of leaks when chest drain is present. More significant leaks occur early – within the first few days and should be explored immediately. Major anastomotic disruptions occur in only 3-5% of leaks, but large leaks can be total and require surgical repair. Mediastinal leaks can lead to TEF recurrence; therefore, they should be monitored carefully.

Fistula Recurrence between the esophagus and trachea is observed in 3-14% of the patients treated for EA/TEF. Fistula usually recurs within a few months, but they may occur as late as 2 years after surgery. An anastomotic leak with local inflammation and erosion at the previous repair site, ischemia and surgical dissection too near the trachea may cause a recurrent fistula. This condition should be suspected when choking episodes occur during feeding and/or when recurrent pneumonia is observed. The best methods of diagnosis are bronchoscopy and oesophagography under videofluroscopic guidance with the patient in prone position and with bolus injections of contrast agent into a nasesophageal tube. Fistula do not close spontaneously and require surgical division and ligation. About 10-20% of cases recur after the first TEF recurrence.

Esophageal Strictures occur in 40% of cases after surgical EA/TEF repair. Strictures result from natural healing as a result of fibrosis, a difference in the sizes of the 2-anastomosed segments, tension and GER. Leaks as well as the use of 2-layer anastomosis and/or silk sutures, enhance stricture formation. Strictures may be diagnosed with barium swallow examination or oesophagoscopy. Although barium swallow study aids stricture reduction by dilatating the anastomotic site, decreasing the size discrepancy between 2 segments and loosening the fibrosis of healing, it is not completely effective and dilatations are required for resolution. Dilatation is 90% effective but strictures that do not respond to dilatation must be surgically resected.

Gastresophageal Reflux is a common complication, occurring in 40-70%of patients after EA repair. Symptoms of GER include coughing, apnea, recurrent pneumonia, failure to thrive and stricture formation. A barium swallow examinations may demonstrate GER, which is caused by tension, dysmotility of the lower esophagus and an altered angle of Hiss due to distal esophageal mobilization. GER may be medically treated by keeping the patient in a prone head-up position after feeding; by thickening the food; by giving smaller and more frequent meals. If problem persists, acid reduction agents such as histamine H2-receptors blockers and prokinetic agents may be administered. If medical therapy is unsuccessfuly, fundoplication may be considered. Fundoplications are required in about half of the patients with GER. GER tends to diminish with time, but long term GER leads to mucosal changes such as Oesophagitis and Barrett Esophagus.

Swallowing Problems due to altered esophageal peritalsis is seen approx. in all patients after EA/TEF repair. Normally, synchronized waves of contraction of the esophagus walls carry food down to the stomach. These are far less organized after EA/TEF repair. This can mean that food is brought back up, making eating enough to keep weight on-alone enough for a child to grow difficult.

Long Gap Esophageal Atresia is finding in small group of children with EA have too large gap in the esophagus to repair straight away. These children have to be tube-fed for some weeks or months until either the gap has decreased enough to permit the repair; or the surgeon decided that the gap will never close sufficiently and alternative part of Gastrointestinal tract must substitute for Esophagus (the stomach, jejunum or colon). In the latter case, sometimes the upper esophagus is brought out into the neck so that the child learns to eat during the time before such an 'Esophageal Substitution Procedure' can be performed. Even though the food will not reach the stomach, this practice *Sham Feeding* makes learning to eat far easier after a functional 'pipe' between the mouth and stomach has been accomplished. A tube is also placed through the skin and body wall into the stomach so that food can be given at the same time. In this way the child learns to associate eating and swallowing with the feeding of a full stomach. The arrangement is called a "cervical esophagostomy and gastrostomy".

Tube Feeding is done in children who have problems with eating (often due to reflux or strictures, as described above) will need to receive some form of tube feeding to supplement their nutrition intake. Here we use either nasogastric tube or gastrostomy to provide food.

Respiratory Problems, because in TEF there is also an abnormality affecting the trachea. Children often suffer respiratory problems – commonly Asthma and repeated infects, also accompanied by the so called 'TEF Cough' – a harsh, barking cough caused by a softness or floppiness (tracheomalacia) of the normally rigid tracheal wall near the site of repair. The floppy trachea can, in some babies, contribute to so-called 'near death' attacks, when the baby goes blue and may pass out. This occurs when the less rigid airway collapses usually at a time when the child makes heavy breathing efforts, for example when crying or coughing. Although it is frightening to observe. Once the child relaxes, the airway opens up and the problems resolve itself. Occasionally surgery may be required in severe cases though this is unusual.

An esophageal substitution causes additional complications. Esophageal replacement has been associated with an increased surgical morbidity rate and a 68% complication rate. These conditions include the following:

- colon: cervical leaks, pulmonary problems, graft necrosis, redundancy ger, anastomotic stenoses, strictures.

In addition colon graft is thin walled and has poor function: subject to pathology (polyps, villous adenomas); slow transit that leads to dilation over patient's life time (this leads to anaemia, poor weight gain, recurrent pulmonary infections and redundancy); intestinal obstruction in 20% of patients; colon graft ulceration in 10% of cases, especially in reterosternal placements (this may lead to barrett's epithelium in the lower esophagus if the lower segment is unused); limited mucosal acid resistance (the colon tends to dilate and form loops).

- gastric tube: frequent leaks and strictures; high incidences of fistulas, stenoses and peptic ulcerations; peptic esophagitis; extensive GER in cervical esophagus, which may lead to peptic ulceration and Barrett epithelium.
- gastric transposition: leakage in 6% cases; stricture at the anastomotic site in 12% of cases; microvasculature easily disturbed with handling; late dialations; long term effects of intrathoracic stomach ulcerations; aspiration.
- jejunum: infarction common; high incidence of peptic ulceration; high free graft failure rate.

Here are the few questions often put by worried parents, so a doctor should always be ready to answer these

Q1. What is a tracheesophageal fistula?

A fistula is a connection between 2 tubes. The breathing tube that connects the nose and mouth with the lungs is called the trachea. The swallowing tube is the esophagus. The breathing tube and the swallowing tube aren't supposed to be connected. But when a child has a tracheesophageal fistula, the fistula connects the 2 tubes. This means that food or milk in the stomach can get into the lungs. This can cause breathing problems and even pneumonia.

Q2. What causes atresia and fistula?

We don't really know what causes these problems. When the esophagus and the trachea grow in the embryo, they start from the same bit of tissue. Sometimes the tubes don't develop right. We don't think these problems are inherited.

Q3. Are these problems common?

About 1 baby out of 4,000 babies has one or both of these problems. They usually occur together. But sometimes a baby has atresia with no fistula.

Q4. How does the doctor know this is what's wrong with my baby?

Most babies with this condition have feeding problems right away. They may spit up a lot or have lots of bubbly mucus in their mouth. If your baby has a fistula, breathing may be hard. If your doctor thinks your baby has one of these conditions, an x-ray can help make the diagnosis.

Q5. How is this problem fixed?

Your baby will need surgery to fix the problem. First, the swallowing tube must be connected to the stomach. Then, if a fistula is connecting the esophagus to the trachea, it must be closed. Your child's doctor will decide when to do the surgery. If the baby isn't premature and doesn't have any other problems (like pneumonia or birth defects), the surgery can usually be done when the baby is just a few days old.

Q6. How long will my baby be sick?

In uncomplicated cases, your baby may be eating by one week after surgery. Meanwhile, until your baby can swallow milk or formula, your baby will be fed through a vein (this is called an "IV") or through a stomach tube. Before regular feeding starts, an x-ray can check for holes at the place the surgeon fixed. However, if your baby was premature, the recovery time might be a little longer. Another factor is how complicated the operation is. If the surgery is harder, it takes a few days longer for your baby to recover. Your baby will stay in the hospital during this time.

Q7. Does my baby have any other problems?

Some babies with esophageal atresia have heart problems, kidney problems, stomach and bowel problems or muscle and bone problems. A physical exam by your doctor, maybe with some other x-ray or ultrasound pictures, will usually show if your baby has other problems. If your baby has other problems, the surgery to fix the swallowing tube might have to wait.

Q8. Will my baby have other problems in the future?

Babies born with esophageal atresia sometimes have long-term problems. Probably the most common problem is gastresophageal reflux disease, what doctors call heartburn. Heartburn is a burning feeling caused by acid that comes up from the stomach into the swallowing tube. It can usually be treated with medicine. Another problem is scar tissue. Sometimes scar tissue grows where the esophagus connects to the stomach. This scar tissue can make swallowing hard or painful because the food can't get past the scar tissue easily. Sometimes another surgery is needed to open the scar tissue. Your child may need more x-rays or endoscopy later. Endoscopy is a way of taking a picture. A narrow tube holding a tiny camera is put into the swallowing tube. The picture helps your doctor see inside the esophagus and stomach.

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PARTICULAR APPLICATIONS OF ELASTIC STABLE INTRAMEDULLARY NAILING (ESIN) FOR FEMORAL FRACTURES IN CHILDREN

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Abstract

Over the past few years there has been a marked increase in the use of intramedullary fixation in the management of fractures of long bones in children. To some extend this reflects a more interventionist attitude among pediatric orthopedic surgeons but is also due to technical developments, notably that of the elastic stable intramedullary nail (ESIN).

We used ESIN for several years for treating transverse or short oblique fractures of long bones in children. We proposed to analyze the utility of this method in treating complex fractures or pathological fractures (not malignant) in children and we reviewed our series of patients treated with ESIN and we found particular cases of femoral fractures treated with ESIN. We analyzed for these patients the type of fracture, age, related conditions and radiographs.

All fractures consolidated in an axial position ($<5^0$ malposition in all planes) with full use of the affected limb. An additional stabilization by plaster casts (6 weeks) was used for the patient with fibrous dysplasia and the patient with long oblique fracture. Partial weight bearing was permitted after the removal of the cast or after 6 weeks for the other patients.

Intramedullary nails have found their place in he management of femoral shaft fractures in children and even more so in adolescents. ESIN should be used as the procedure of choice for treating femoral fractures in children for many reasons including the economic reason.

Keywords: femoral fracture, ESIN, pathological fracture, child, osteosynthesis

Introduction

Over the past few years there has been a marked increase in the use of intramedullary fixation in the management of fractures of long bones in children (1). To some extend this reflects a more interventionist attitude among pediatric orthopedic surgeons but is also due to technical developments, notably that of the elastic stable intramedullary nail (ESIN).

In 1979, physicians of the French school of Prevot in Nancy started using an elastic stable intramedullary system for femoral shaft fractures in children (1;2). The elastic nails of the French school were an analogous evolution to the stable elastic osteosynthesis proposed by a Romanian group in 1981 (3). In Metaizeau's 1988 monograph (4), the Nancy group describe the physiologic and biomechanical background for using the "embrochage centro medullaire elastique stable" (ECMES) system, the elastic stable centromedullary nailing system with its three-point pressure stabilization of the fractured bone.

Previous experience had suggested that elasticity and stability were not easily combined in one construct (5). However, working from the concept of three-point fixation, these surgeons were able to improve stability significantly by using two pre-tensioned nails inserted from opposite sides if the bone. Metaizeau (2) and his colleagues were able to show that titanium nails, which were accurately contoured and properly inserted, could impart excellent axial and lateral stability to diaphyseal fractures in long bones. Rotational stability was also better than had previously been experienced, although this was to remain the weakest point of the technique (5).

ESIN gives not a rigid but rather an elastic stability. This stimulates the fracture callus. An important advantage comes from the fact that the fracture site is not opened, there is no blood loss and the periostium retains its regenerative power. All of these factors contribute to rapid consolidation (6). If the right size nails are chosen, there is enough rotatory stability and the patients are allowed to bear weight as early as they choose. These factors also contribute to rapid consolidation. With an adequate size of nails there is enough rotatory stability and the patients can be allowed early weight bearing (4).

The ideal fracture for this technique is a transverse or short oblique diaphyseal fracture with minimal comminution in a long bone. However, such is the versatility of the method that the indications have widened considerably with time and personal experience (5). These fractures are easiest to nail and the results are generally good. However, if one is prepared to accept some operative difficulties, all types of fractures can be efficiently stabilized with ESIN with appropriate experience. It is advisable to first gain sufficient expertise with transverse fractures before embarking on nailing spiral fractures. Subsequently fractures with a butterfly fragment may be attempted and finally complex comminuted fractures (7).

For children with neuromuscular conditions or bone fragility, the period of immobilization must be kept to a minimum. Although the quality of bone healing may be uncertain in these patients, ESIN remains superior to plating. The nails function as a splint and protect bone from

chronic deforming. The sliding constructs have definitive advantages here (7).

Purpose

We used ESIN for several years for treating transverse or short oblique fractures of long bones in children. We proposed to analyze the utility of this method in treating complex fractures or pathological fractures (not malignant) in children.

Materials and method

From 2002 we used ESIN as the procedure of choice for children's fractures in our department.

We reviewed our series of patients treated with ESIN and we found particular cases of femoral fractures treated with ESIN. We analyzed for these patients the type of fracture, age, related conditions and radiographs (Table 1).

Surgical technique

Longitudinal skin incisions 2 to 3 cm long are made on the lateral and medial aspects of the distal femoral metaphysis at the level of the upper border of the patella. The entry hole into the bone is made using an awl about 2 cm above the distal growth plate of the femur.

It is preferable to introduce the first nail o the side where the fragments overlap (Fig. 1).

Table 1. Synopsis of patients

Age at operation	*Diagnosis*	*Type of implants used*	*Period of implant*	*Result*	*Removal of implant*
6 yrs	Fracture in the proximal third of the left femur. Fibrocystic dysplasia	K-wires	6 months (1 nail removed after 2 months because of distal migration)	Solid union	Yes
9 yrs	Pseudarthrosis of the middle third of the right femur after early removal of Kuntscher rod for femoral fracture	Elastic nails	1 nail removed after 6 weeks because of wrong direction in the proximal fragment)	Solid union after 2 months	No
15 yrs	Long oblique fracture in the middle third of left femur	Elastic nails	-	Solid union after 2 months	No (lost at follow-up)
15 yrs	Juvenile bone cyst (JBC) of the right femoral neck	Elastic nails	-	Slow healing of the JC	No

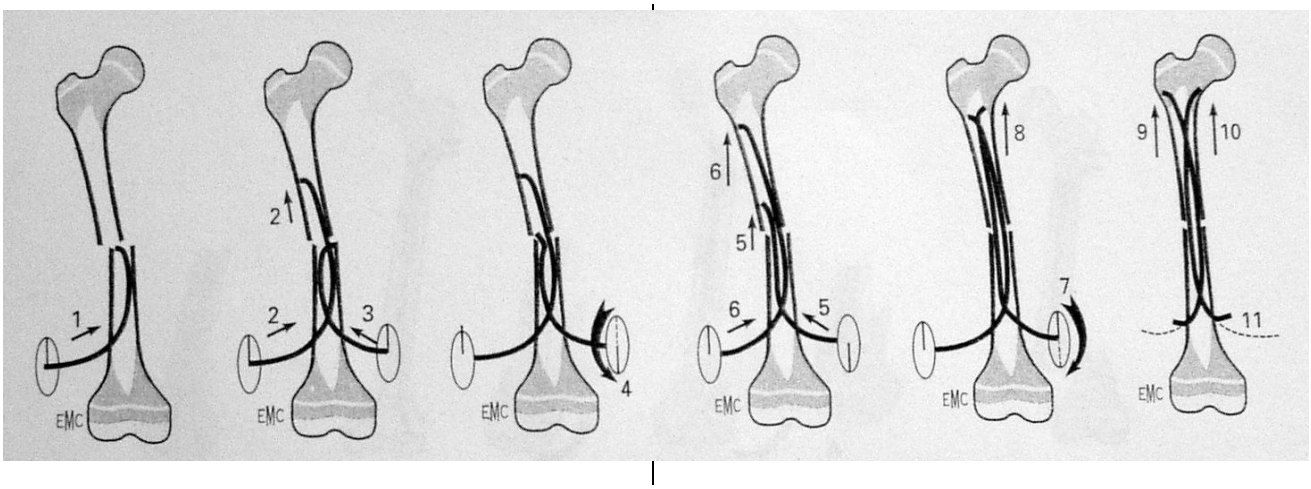

Fig. 1. 1. Introduce the nail on the side where the fragments overlap; 2. The first nail is pushed through the fracture site; 3. The second nail is introduced into the medullary canal; 4. The tip of the second nail is directed toward the fracture site; 5. The second nail is pushed through the fracture site; 6. The first nail is pushed upwards; 7. The second nail is re-orientated; 8. Both nails are pushed near the metaphysis but do not penetrate the cancellous bone; 9. and 10. After reduction of the fracture, the two nails are introduced into the cancellous bone of the metaphysis; 11. The bases of the nails are bent 90^0 and cut. After (7)

It is hammered up the medullary canal to within a few millimeters of the fracture. Under image intensification, the tip of the nail is directed by an axial twist across the fracture site. The second nail is inserted in a similar fashion. Both nails are directed so that they diverge superiorly. The quality of reduction is controlled radiographically. If angulation persists, it is corrected by external manipulation. The traction is removed and the two nails are impacted into the cancellous bone of the proximal metaphysis.

The bases of the nails are bent to 90^0 at the level of the lower metaphysis and cut to leave 1 to 1.5 cm beneath the skin.

The skin is closed. Before waking the patient up the knee is flexed to 90^0 to sink the nails into the fibers of the vastus medialis and lateralis and to avoid stiffness of the knee.

It is essential to ensure that there is no malrotation by assessing the internal and external rotation of the hip. If there is significant difference between the two hips, the child must be repositioned and the nailing redone. The nails are withdrawn so that they lie free within the medullary canal. After manually correcting the malrotation they are again impacted into the proximal cancellous bone.

Finally, a compression bandage is applied around the thigh and knee.

Results

All fractures consolidated in an axial position ($<5^0$ malposition in all planes) with full use of the affected limb. An additional stabilization by plaster casts (6 weeks) was used for the patient with fibrous dysplasia and the patient with long oblique fracture. Partial weight bearing was permitted after the removal of the cast or after 6 weeks for the other patients.

All patients had an unrestricted quality of life, due to the minimally invasive technique of the operation.

The desired formation of callus appeared in all patients, no pseudarthrosis was observed so far.

As expected, the time of consolidation of the pathological fracture and pseudarthrosis was distinctly longer than with normal fractures, which usually have an average of 6-8 weeks. Occasionally the implants were left in situ for more than two years without any visible negative effect on the growth of the affected limb. During growth the end of he nails may migrate into the metaphysis of the corresponding bone without radiologically visible irritation. Nails that become too short can be exchanged for longer and stronger implants.

We had 2 complications: wrong trajectory of one nail in the case of pseudarthrosis (which required removal after 6 weeks) and distal migration of the nail in the case of fibrous dysplasia (required removal after 2 months).

Other complications such as growth disorders, infection or problems with soft tissues were not observed.

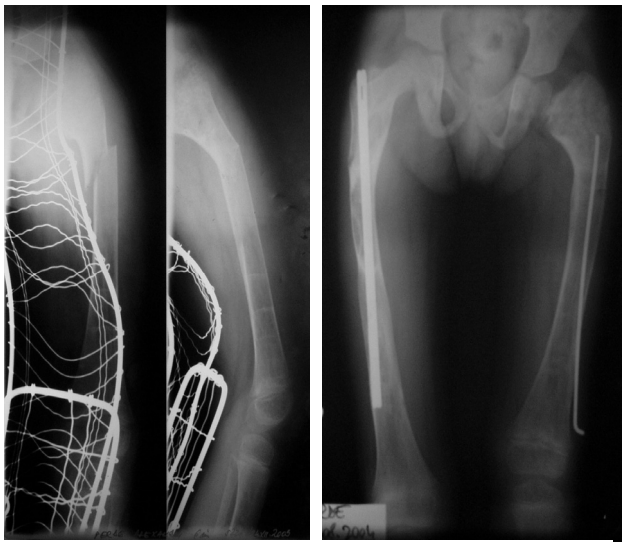

Fig. 2. Fracture in the proximal third of femoral shaft. Fibrous dysplasia. After union and removal of one nail because of distal migration.

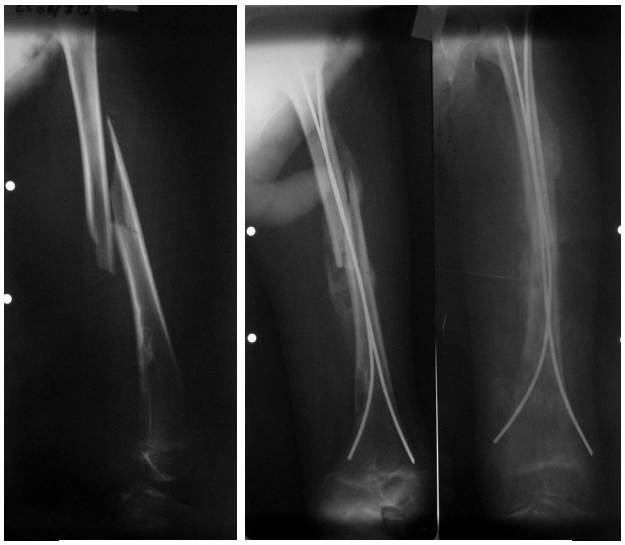

Fig. 3. Long oblique fracture of the left femur (before and after nailing and union).

Discussions

Intramedullary nails have found their place in he management of femoral shaft fractures in children and even more so in adolescents (8;9).

There are two prerequisites if closed intramedullary nailing is planned: an orthopedic fracture table and an image intensifier. An orthopedic traction table with child-size shoes is advised for every closed treatment of femoral shaft fracture, whether the surgeons uses the extra- or the intramedullary system (9;10). An image intensifier is necessary for the closed reduction and fixation of a femoral shaft fracture.

Insufficient alignment of the fracture sometimes is a problem with elastic nails (10), especially in fractures with deficient bone marrow, as in osteogenesis imperfecta or myelodysplasia (8).

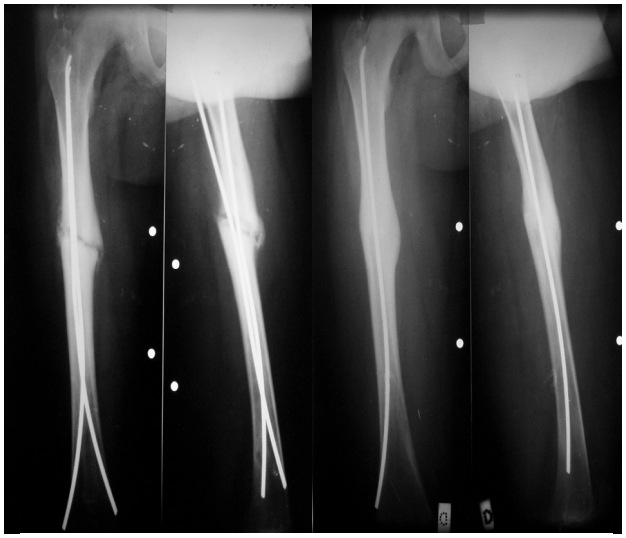

Fig. 4. Pseudarthrosis of the right femur. Solid union after removal of one wrong direction nail.

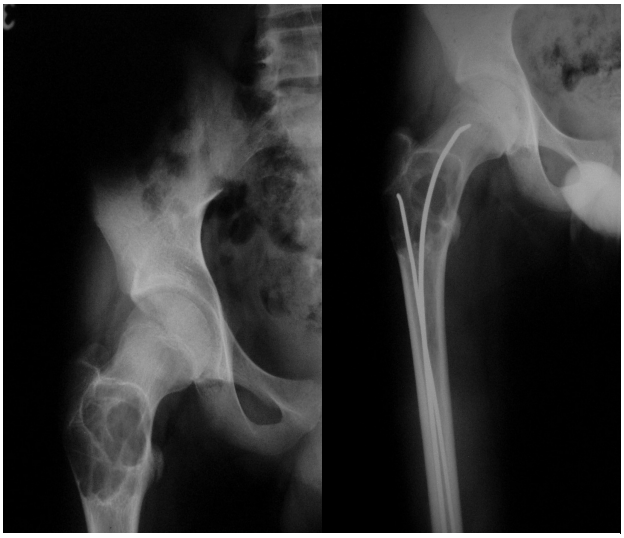

Fig. 5. Juvenile bone cyst of the right femoral neck. Recession of the cyst after nailing (the elastic nails act as internal splint and serve for cyst decompression).

Local skin irritation at the distal femoral insertion site of the rods has been observed after using Nancy nails. In Nancy, 13 of 123 patients (9) and in Munich 2 of 54 children needed secondary shortening of the nails (6). In Stuttgart Parsch observed 8 skin irritations in 45 cases that necessitated shortening of the nail (6). Since the introduction of the new nails with olives, this problem disappeared.

Knee mobility may be reduced in the early phase after the introduction of elastic nails. Parents must be warned about this to avoid unnecessary worries. The limitation of knee flexion disappeared rapidly in all cases after pins were removed (6).

Elastic stable intramedullary nailing has several advantages (11):

- The operation can be done through small incisions, without significant trauma to tissue;
- The reduction is performed as either a closed or an open procedure, thus the pathological bone area may be exposed and, if required, biopsied. The fracture haematoma, the periost and the surrounding soft tissue are spared to encourage accelerated formation of callus;
- The system is elastic and not stiff, thereby rapidly inducing callus with subsequent secondary fracture-healing;
- The metal nails can be left in place without negatively affecting the healing of the bone disease, since, according to the prevailing opinion in the literature, no negative influence on the growth of the affected bone has been demonstrated to date;
- The removal of the implants is simple, quick and atraumatic.

Elastic nails have a useful role in the management of benign pathological fractures of long bones. The pathological fracture may be as a result of local bone weakness or more generalized pathology.

Asymptomatic defects such as fibrous cortical defects or unicameral bone cysts can present as a fracture (12;13). In general, these fractures will unite and often cyst itself will heal. The fracture can be treated by conservative methods but use of elastic nails has some advantages. As well as the stabilization of the fracture the nails will decompress the cyst (11;14;15), which will promote healing of the defect as the fractures unites.

The most common cause of generalized bone weakness resulting in fractures is osteogenesis imperfecta. As well as presenting with an acute long bone fracture, osteogenesis imperfecta also results in progressive bowing of the long bones as a result of repeated micro-fractures. Elastic nails can be used to manage the acute fracture and also to stabilize corrective osteotomies.

Particular care should be exercised in the use of ESIN in osteogenesis imperfecta. Perforation through the abnormal cortex may easily occur and the medullary canal may be very narrow. It is recommended that as long a nail as possible be used and it may be necessary to perform exchange nailing as the child grows. Bending the end into a hook will prevent the nail from being pulled into the bone with subsequent growth. The nails should be left in place at least until the end of skeletal growth.

Conclusions

Elastic stable intramedullary nailing, as a minimal invasive procedure, appears to be safe and reliable method that has good long-term results in the treatment of femoral fractures in children aged 3-15 years. This method has advantages and disadvantages but the overall results make them superior to both traction and cast, in the period of minimal invasive procedures' advent in pediatric orthopedics. For social, psychological and economic reasons, it is time to abandon traction and cast as treatments for femoral fractures in children.

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UNDESCENDED TESTIS TREATMENT: PERSONAL RESULTS VERSUS LITERATURE DATA

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Abstract

The undescended testis is a term we use to describe all instances in which the testis cannot be manually manipulated into the scrotum. Electron microscopy has confirmed reduced number of spermatogonias and tubular diameter in undescended testis after the first two years of life. To improve spermatogenesis treatment should be done before the age of two. Other reasons to realize orchidopexy are: a higher incidence of malignancy, trauma and torsion, and future cosmetic and psychological problems in the child. The management is surgical and/or hormonal (Human Chorionic Gonadotropin - HCG). Surgery is limited by the length of the testicular artery. Palpable testes have a better prognosis than non-palpable. This paper work presents the personal results of undescended testis treatment compared to the most important studies in a chronological order.

Key words: undescended testis, hormonal treatment, surgical treatment.

Introduction

Undescended testis is a common congenital abnormality occurring in 2-5% of full-term boys at birth (the incidence is double at preterm infant). By 3 months of age, the incidence rate spontaneously reduces to 1-2%.

The etiology of the disorder is not very well known, but the integrity of hypothalamo-pituitary-gonadal axis is needed for normal descent of the testes. Abnormal sexual differentiation is associated with maldescent and the majority of boys with undescended testis show no endocrine abnormalities after birth.

Several studies have been performed to evaluate the ultra-structure of the undescended testis after birth. Increased degeneration of germ cells can be observed in undescended testes after the first year (electron microscopy). From the age of 2 years, changes which occur in the undescended testis can be found on light microscopy with a qualitative difference in the changes the higher the testis lies, and therefore early treatment is recommended. So most pediatric urologists recommend orchiopexy by 1 to 1.5 years of age or earlier, because fertility potential may be improved by early treatment. Other reasons to treat are to avoid testis cancer and psychological reasons. The most effective treatment is surgery, but hormone treatment with either hCG or GnRH analogues can be considered, particularly in cases where testes can be palpated in high scrotal position. The efficacy of hormone treatment depends on the initial location of the testis; nonpalpable testes rarely descend with hormone treatment. However, both surgery and hormone treatment can have untoward effects. Treatment with hCG has been associated with an inflammation-like reaction in the testes and an increased rate of apoptosis of germ cells leading to a reduced adult size of the testes. Vascular complications can occur during surgery, particularly in staged orchidopexies.

Purpose

The aim of study is to establish correlations between the results of hormonal and surgical treatment on 206 cases of undescended testis hospitalized from January 2002 to December 2004 at Clinical Emergency Hospital for Children "Louis Turcanu" Timisoara, Department of Pediatric Surgery, and the most recent literature data.

Material and method

The necessary data to elaborate personal study was obtained by analyzing the observation files, laboratory results and surgical protocols. The literature data was obtained from on line prestigious journals of pediatric surgery.

Results

From 01.01.2002 to 31.12.2004 a number of 206 patients with undescended testis were treated at Clinical Emergency Hospital for Children "Louis Turcanu" Timisoara, Department of Pediatric Surgery, and an approximative constant distribution of cases / year was found (fig. 1).

Place distribution of cases indicated that the urban area had slightly more cases, probably because of better development of medical services and more facile access to them (fig. 2).

According to localization right side undescended testis was found in half of cases, almost 1/3 cases on left side and in 1/5 cases both testicles were in a high position (fig. 3).

year 2002 – 64 cases

year 2003 – 73 cases

year 2004 – 69 cases

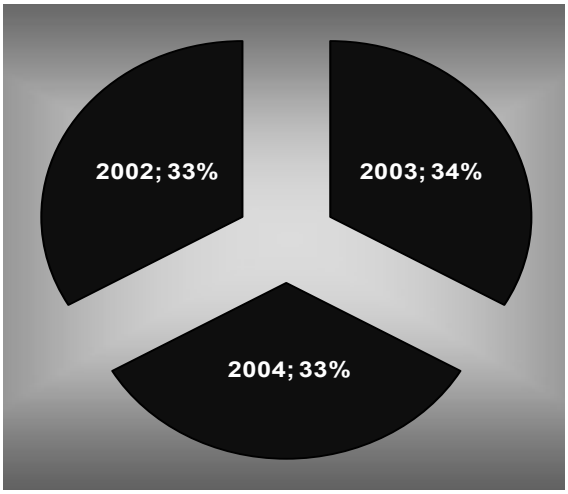

Fig. 1. Annually repartition of undescended testis cases.

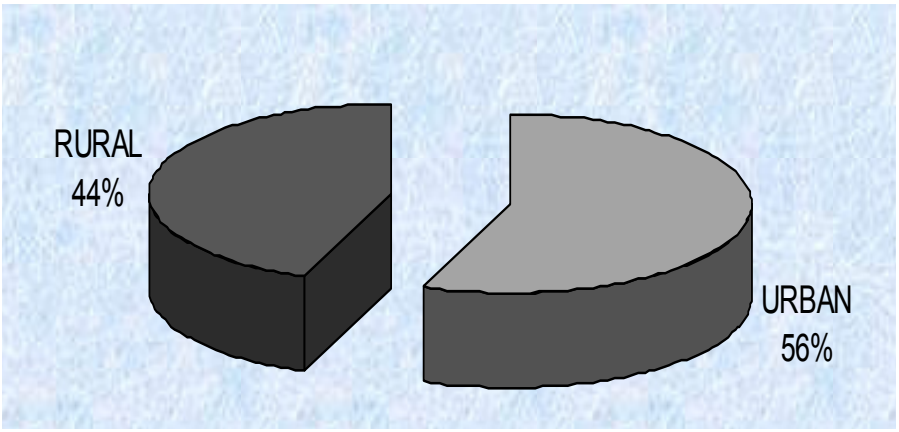

Fig. 2. Place distribution of cases.

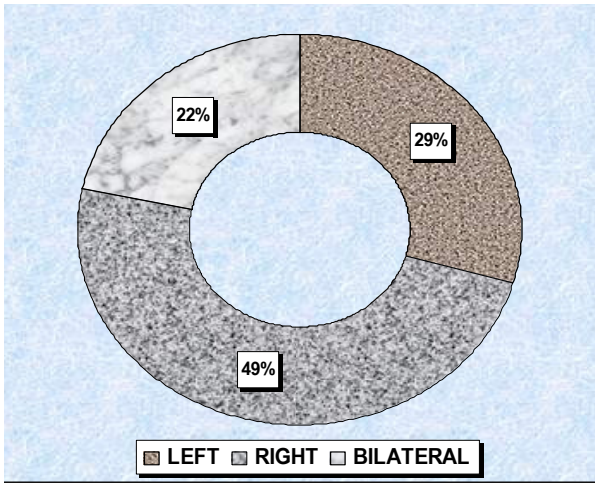

Fig. 3. Distribution of cases according to localization.

If we refer at age of diagnosis, we found the following results:

- 0 – 12 months – 7 cases
- 1 – 4 years – 69 cases
- 5 – 10 years – 96 cases
- 11 – 16 years – 44 cases

We can observe that only 3% of cases were resolved under age when histological modifications occur, 32% of cases between 1 and 4 years, 45% case at group 5-10 years and 20% after 11 years old (fig. 4).

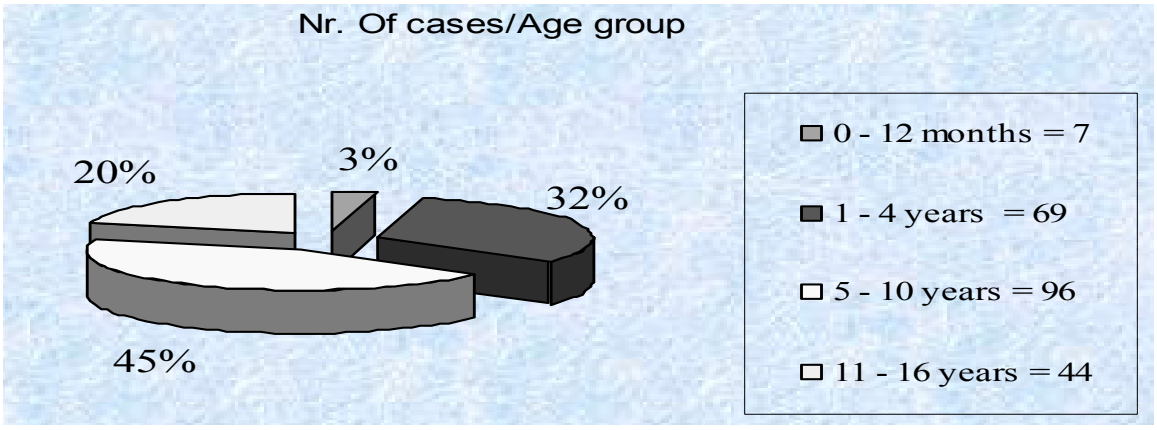

Fig. 4. Repartition of cases according to age group.

If we consider the therapy, next table presents the treatment methods:

TREATMENT	2002	2003	2004	TOTAL
HORMONAL	6	11	9	26
SURGICAL	51*	49*	52*	152*
HORMONAL + SURGICAL	7	13	8	28

*2, 5 respective 4 cases (total 11) needed two stage orchidopexy

It is important to mention that the hormonal therapy was made by OMS indications which mean: 250 UI HCG at age < 1 year, 500 UI HCG at age 1-5 years and 1.000 UI HCG at patients older then 5 years, 10 doses (2 doses per week for 5 weeks).

We can observe that the number of successful results (12,5%) is equal with cases which surgical interventions after hormonal treatment.

If we refer to literature data, many authors have been preoccupied of the modifications of the hormonal table and fertility at patients treated formerly of undescended testis. Although there are many contradictory opinions, I'll present the most important studies developed in the last 5 years, in a chronological order.

Crespo Chozas and collaborators, in 1999, studied 20 postpubertal males with a mean age of 17.35 years (range: 15-21 years) and treated for undescended testis during childhood were evaluated for pubertal development and gonadal function. A hormonal study which included basal determinations of testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and semen analysis was performed on each patient. Complete virilism was observed in all patients. The start and development of puberty were normal in all cases (except one patient that started puberty at 10 years of age). Basal studies in all patients showed normal levels of LH and testosterone. FSH levels were increased in 3 patients and normal in the other 17 patients. Fourteen patients achieved normal spermatogenesis with more than 20 million spermatozoids/ml. In the other 7 patients (35%), 5 with unilateral undescended testis and 2 with bilateral undescended testis, the sperm count remained below 20 million with a range of 0.8 to 18.4 x 10^6 spermatozoids/ml. The three males with elevated levels of FSH also presented oligospermia. The results showed that pubertal development is normal after undescended testis. Impaired spermatogenesis was a major factor in undescended testes. Basal FSH levels can be useful in predicting germinal damage secondary to undescended testis.

In the same year, Lee PA and collaborators studied 84 men with a history of unilateral undescended testis. They found that age at orchidopexy significantly correlated inversely with inhibin B and positively correlated with FSH. Comparison of mean hormone levels and sperm density by analysis of variance for linear trend revealed a significant relationship between age at surgery with inhibin B and testosterone, while sperm density, FSH and luteinizing hormone were not significantly related. Men

who previously had unilateral undescended testis and who underwent orchidopexy by age 2 years have higher inhibin B and lower FSH profiles than those who underwent surgery later in life. This finding suggests an overall beneficial effect of early orchidopexy in boys born with unilateral undescended testis.

The same authors compared sperm counts and gonadotropin levels before and after gonadotropin-releasing hormone stimulation between formerly unilaterally cryptorchid men and controls that had completed a detailed questionnaire on fertility and other pertinent paternity information. These parameters were also compared between the subsets of formerly cryptorchid men who reported paternity and unsuccessful attempts at paternity. Sperm density and total count, and basal and gonadotropin-releasing hormone stimulated follicle-stimulating hormone (FSH) levels were different in the undescended testis and control groups. Higher FSH levels and lower sperm counts correlated inversely in the undescended testis group, while luteinizing hormone, testosterone and other results of semen analysis did not differ. Furthermore, FSH levels were higher and sperm counts were lower in the subset who reported unsuccessful attempts at paternity compared with those reporting paternity. Other measured parameters did not differ between these groups. They concluded that FSH levels are significantly higher and sperm counts are significantly lower in formerly cryptorchid men than in controls. In the undescended testis group the same differences are found in fertile and infertile men. Thus, elevated FSH and low sperm counts may be considered risks for infertility in formerly cryptorchid men.

In 2000, the same authors, determined differences in paternity and levels of the hormones inhibin B, follicle-stimulating hormone, luteinizing hormone, testosterone and free testosterone based on the preoperative location of the undescended testis in men with previous unilateral undescended testis. In 103 cases they performed semen analysis and measured the levels of the hormones inhibin B, luteinizing hormone, follicle-stimulating hormone, testosterone and free testosterone. Paternity, sperm count and hormonal parameters were compared with cryptorchid testicular location. Logistic regression was done to analyze pre-treatment testicular location as a risk factor for infertility. Paternity, duration of attempted conception in men who achieved paternity, sperm count and hormone levels did not differ based on abdominal, internal ring, inguinal canal, external ring, upper scrotum or ectopic testicular location. The overall paternity rate was 90% with the lowest rate of 83.3% in the abdominal group. More than 12 months were required to achieve conception in 28.9% of the study group overall and in 39.4% of the abdominal group. Varicocele and a partner with fertility problems were risk factors for infertility, while abdominal testicular location caused borderline significant risk. They concluded that preoperative testicular location in men with previous unilateral undescended testis is not a major determinant of fertility according to paternity, sperm count or hormone levels.

In 2001, in Italy, Vinardi S and collaborators evaluated testicular volume, serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone as well as semen specimens, in 57 men (mean age, 19 years; range, 18 to 27 years) treated in childhood for unilateral (n = 47) and bilateral (n = 10) undescended testis. In 3 unilateral cases monorchidism was found. Thirty-seven patients underwent orchidopexy after hormonal treatment (luteinizing hormone releasing factor, 1.2 mg/d for 28 days followed by human chorionic gonadotropin, 500 IU intramuscularly 3 times a week for 3 weeks). The remainder underwent surgery. Mean age at surgical treatment was 5.4 years (range, 2 to 12 years). These patients were examinated again after a mean period of 13.3 years (range, 10 to 19 years). Reduced testicular volume (<12 mL) was found in 6 of 64 testes (9.3%). LH, FSH, and testosterone levels were found within the normal range in all patients. With linear regression, inverse relations were found between FSH and, respectively, testicular volume, sperm concentration, sperm motility, and normally shaped sperms. There were direct relations between testicular volume and sperm concentration, sperm motility, and normally shaped sperms. They did not find any statistical correlation between age at surgery and semen quality. Significantly better results in terms of sperm counts were found in patients directly operated on in comparison to those treated with hormones before orchidopexy.

Cortes D and collaborators studied 135 patients with undescended testis (70 bilateral and 65 unilateral) in 2003, who had a simultaneous biopsy taken at orchidopexy in childhood, and in adulthood had analyses of semen and FSH. In adulthood 42 formerly bilateral cryptorchid boys had repeat testicular biopsies taken. Infertility was suspected in men with < 5 million sperm/mL in the best sample of semen and concomitant poor sperm motility, and who were classified by follicle-stimulating hormone (FSH) values. At orchidopexy the number of spermatogonia/tubule and the germ cell differentiation were measured. In adulthood the percentage of tubules with complete spermatogenesis, spermatogenic arrest and Sertoli-cell only status was assessed. Infertility was suspected in 38 of 70 (54%) of formerly bilateral and six of 65 (9%) formerly unilateral cryptorchid patients. High FSH values were expected in these suspected infertile patients, but 15 of 38 (59%) formerly bilateral and five of six formerly unilateral cryptorchid patients had normal FSH values. These patients were identified in childhood at orchidopexy; those with bilateral undescended testis generally presented with germ cells, but the mean number of spermatogonia per tubule was < 30% of the lowest normal value, and the germ cells were seldom normally differentiated, whereas those with unilateral undescended testis generally lacked germ cells in the biopsies. No patients had a decreased FSH value.

Conclusions

By analyzing these studies the conclusion is that the level of testosterone and LH, in the majority of the cases of undescended testicle, is in normal limits, while FSH levels modifies in connection to fertility. So, while oligospermia is high, FSH values are high too. The infertility rate is 50% in some studies, when the disease is bilateral and 10% when it is unilateral. There are no major

influences regarding the initial position of the undescended testicle, but the best results were obtained in the case of orchidopexy until the age of 2 years.

Although our knowledge on undescended testis has increased considerably during the last decades, many questions about undescended testis treatment and its results remain to be answered:

1. Do hormones have any role in the treatment? In our opinion they do, 12,5% of cases in our study being healed with hormonal treatment only.

2. What is the role of surgical treatment? Surgical treatment is the most effective and reliable method to bring testes into the scrotum.

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MINIMALLY INVASIVE TREATMENT OF A FEMUR BONE CYST WITH PERCUTANEOUS AUTOGENOUS BONE MARROW INJECTION CASE REPORT

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Abstact

The management of a unicameral bone cyst varies from percutaneous needle biopsy, aspiration and local injection of steroids, or demineralized bone matrix, to the more invasive surgical procedures of conventional curettage and grafting or subtotal resection with bone grafting. The best treatment for a unicameral bone cyst is yet to be identified. Better understanding of the pathology will change the management concept. The aim of this treatment is to prevent pathologic fractures, to promote cyst healing, and to avoid cyst recurrence and re-fracture. We present a case in which the management of the bone cyst was local injection of bone marrow. Percutaneous bone marrow injection is an effective method for managing simple bone cysts and it might be considered before the application of more extensive procedures.

Key words: bone cyst, percutaneous needle biopsy, percutaneous bone marrow injection.

Introduction

The nicameral bone cyst is a relatively common lesion of the child's bone. It appears to originate from the growth plate and represents a failure of ossification and remodeling of the metaphyseal bone. Cysts contiguous with the growth plate are classified as active cysts; cysts with bone intervening between the lesion and the growth plate are inactive.

The proximal humerus and the proximal femur account for 90% of cases of unicameral bone cyst.

The failure of metaphyseal remodeling accounts for an increased width of the bone at the site of the cyst, but the diameter is not larger than that of the physis. The cyst is surrounded by a thin rim of bone.

The majority of simple bone cysts (SBC's) is not symptomatic and remains undiagnosed or is discovered by accident. A number of simple bone cysts are only diagnosed after a pathological fracture which occurs as a presenting symptom.

Treatment is only indicated to prevent pathologic fracture of the bone. If the percentage of bone occupied by the cyst is > 85% in both radiographic planes, the risk of fracture is high, and spontaneous healing usually does not occur. The diagnosis is based on characteristic radiography.

The success rate following open procedures has ranged from 55% to 65%.[13]

The remaining 35% to 45% of patients have had recurrence of the cyst, requiring additional open surgical procedures. As a result of the high reoperation rate and considerable morbidity associated with such procedures, alternate methods of treatment have been pursued.[13]

Case presentation

We present a case of a years old boy that was admitted in our department for pain in the region of the upper knee. The diagnosis was established after an x-ray examination was performed. The images are shown below (fig. 1).

The bone cyst was treated with the injection of bone marrow in the operating room, with the patient under general anesthesia and with a sterile technique.

A cystogram was made by placing a gauge bone-marrow needle into the inferior portion of the cyst. The aspiration of the cyst revealed sero-sanguinous fluid and contrast material.

Trepanation of the cyst was then performed by placing a second gauge needle into the most superior portion of the cyst.

Bone marrow was then aspirated from the anterior iliac crest with a gauge spinal needle as showed in the pictures bellow. The amount of bone marrow injected into the cyst was the same as the amount aspirated previously from it. In this case 30 ml of bone marrow was injected into the cyst.

Placing the needles far apart from each other, at the extreme ends of the cyst, is an important technical point. Most of the recurrences develop at the ends of the cyst and may have been related to incomplete filling of the ends of the cyst.[13]

Persistently pulsating bloody fluid should not be encountered with a unicameral bone cyst. If it is, an open biopsy should be done to rule out other neoplastic entities such as an aneurysmal bone cyst or a sarcoma. [13]

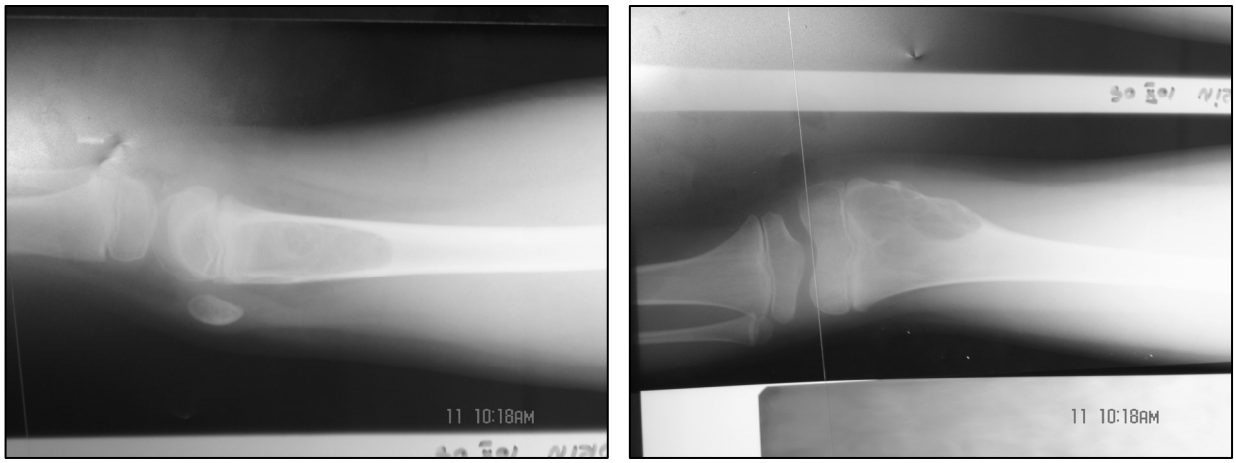

Fig. 1 The radiological aspect of the femur cyst.

If a lesion does not fill completely after the injection of the contrast material, an open biopsy should be performed to confirm the diagnosis. After a fracture has occurred through a cyst, the cyst may be multiloculated and may require the use of more than two needles.[13]

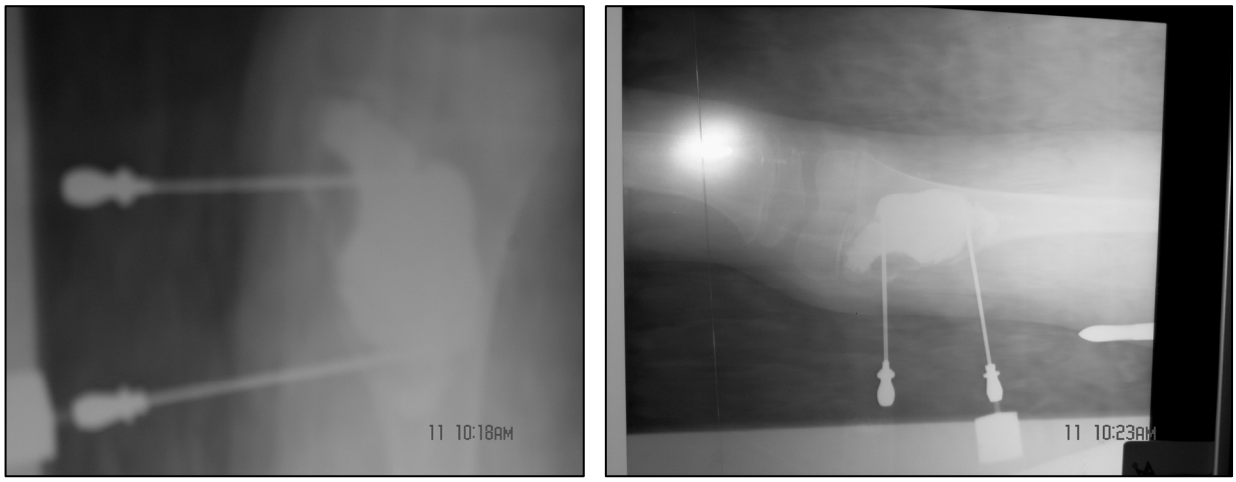

Fig. 2 Percutaneous puncture of the cyst at two ends.

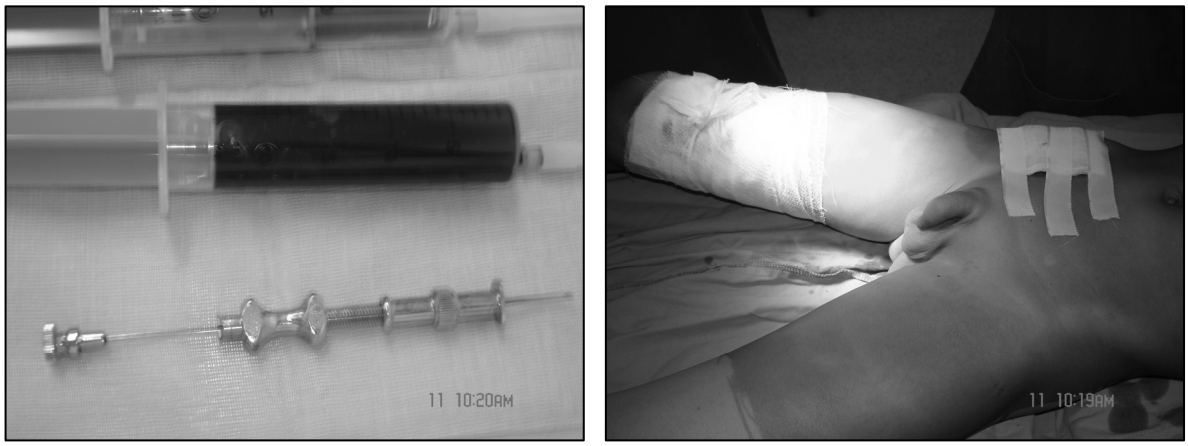

Fig. 3 The instruments used,amount of bone marrow harvested and the site where the bone marrow was harvested from.

Many authors recommend that the patients should be assessed five weeks after the injection; they then be followed radiographically every three months for two years and then every six to twelve months thereafter.

Rougraff et al. [7] reported that successful treatment was achieved with one injection in 78% of patients and with two injections in all patients. They did not observe any fractures of non-enlarging lytic bone defects associated with incomplete bone-healing following treatment. There were no late recurrences of any of the cysts reported by the authors.[7]

Kanellopoulos et al. [2], reported the successful treatment of 19 patients (mean age 10 years) with active unicameral bone cysts using a combination of percutaneous reaming and injection of a mixture of demineralized bone matrix and autologous bone marrow.[2]

The follow-up ranged from 12 to 42 months (mean 28 months). All patients were asymptomatic at the latest follow-up. Two required a second intervention to accomplish complete cyst healing. The radiographic outcome was improved in all patients according to the Neer classification at the latest follow-up. There were no significant complications related to the procedure, nor did any fracture occur after the initiation of the above regimen. [2]

Docquier et al. [4] presented, in their study, the results of this treatment in 21 simple bone cysts with a high risk of fracture. Slow regression of the cyst and progressive healing were obtained in 15 cases (71.4%), whereas no response was noted in 3 cases (14.3%) and recurrence in another 3 (14.3%), after a mean follow-up of 37.1 months.[4]

Yandow et al. [10] reported a study of 12 patients with the following results ; eight (67%) patients demonstrated substantial healing, two (17%) showed partial healing, and two (17%) did not respond to bone marrow therapy.[10]

The advantages of bone marrow injection over the currently practiced methods include a higher success rate with a single injection and earlier healing.[10]

In conclusion the percutaneous injection of autogenous bone marrow is an effective treatment for active unicameral bone cysts.

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MANUSCRIPT REQUIREMENTS

The manuscript must be in English, typed single space, two columns (equal width – 8,5 cm, line between and spacing – 0,8 cm) on A4 paper, with margins: top – 3 cm, bottom – 2,26 cm, left – 1,5 cm, right – 1,7cm. A 10-point font Times New Roman is required.

The article should be organized in the following format: Title, Names of all authors (first name initial, surname), Names of institutions in which work was done (use the Arabic numerals, superscript), Abstract, Keywords, Text (Introduction, Purpose, Materials and Methods, Results, Discussions and/or Conclusions), References, first author's correspondence address.